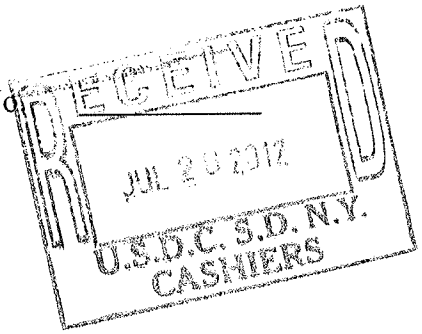
IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

PURDUE PHARMA L.P. and GRÜNENTHAL GMBH, Plaintiffs, v. ACTAVIS ELIZABETH LLC, Defendant.	12 CV 5615 C.A. No.



COMPLAINT

Plaintiffs Purdue Pharma L.P. and Grünenthal GmbH for their Complaint herein, aver as follows:

NATURE OF THE ACTION:

1. This is an action for patent infringement arising under the patent laws of the United States, Title 35, United States Code, and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

THE PARTIES: PLAINTIFFS

2. Plaintiff Purdue Pharma L.P. ("Purdue Pharma") is a limited partnership organized and existing under the laws of the State of Delaware, having a place of business at One Stamford Forum, 201 Tresser Boulevard, Stamford, CT 06901-3431. Purdue Pharma is an exclusive licensee of United States Patent No. 8,114,383 identified in paragraph 10 below. Purdue Pharma is also the holder of New Drug Application ("NDA") No. 022272 for the controlled-release oxycodone pain-relief medication OxyContin®, and is involved in the sales of OxyContin® in the United States.

3. Plaintiff Grünenthal GmbH ("Grünenthal") is a corporation organized and existing under the laws of Germany, having an address at 52078 Aachen, Zieglerstrasse 6, Germany. Grünenthal is the owner of United States Patent No. 8,114,383 identified in paragraph 10 below.

THE PARTIES: DEFENDANT

4. Upon information and belief, Defendant Actavis Elizabeth LLC ("Actavis") is a limited liability company organized and existing under the laws of the State of Delaware, having its principal place of business at 200 Elmora Avenue, Elizabeth, NJ 07207.

5. Upon information and belief, Actavis is registered as a Pharmacy Establishment in the State of New York by the New York State Department of Education, Office of the Professions. (Registration No. 025892). The Registration has an active status and is valid through February 28, 2015.

JURISDICTION AND VENUE

6. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201 and 2202.

7. This Court has personal jurisdiction over Actavis because, *inter alia*, Actavis has purposefully availed itself of the rights and benefits of the laws of this State and this Judicial District. Upon information and belief, Actavis does business in this State and this Judicial District, has engaged in continuous and systematic contact with this State and this Judicial District, and derives substantial revenue from things used or consumed in this State and this Judicial District. Upon information and belief, Actavis engages in the manufacture and sale of a range of pharmaceutical products within and directed to the United States, this State, and this Judicial District specifically. Actavis did not contest personal jurisdiction in this Judicial District in patent litigation concerning United States Patent Nos. 6,488,963, 7,674,799,

7,674,800, 7,683,072, and 7,776,314, which suit was based on the same Abbreviated New Drug Application ("ANDA") No. 202434 described in paragraph 10 below that Actavis submitted to the FDA based on Purdue Pharma's OxyContin® NDA No. 022272. *See Purdue Pharma L.P. et al. v. Actavis Elizabeth LLC*, No. 11-civ-2038 (SHS) (S.D.N.Y. Mar. 23, 2011). Further, this Court has personal jurisdiction over Actavis because Actavis is registered as a Pharmacy Establishment in the State of New York by the New York State Department of Education, Office of the Professions. In addition, upon information and belief, Actavis is actively preparing to make the proposed generic copies of OxyContin® that are the subject of its ANDA No. 202434, and to use, sell and offer for sale such generic copies in this State and this Judicial District.

8. Venue is proper in this Judicial District under 28 U.S.C. §§ 1391(b) and (c) and § 1400(b).

THE PATENT IN SUIT

9. Grünenthal is the lawful owner of all right, title and interest in United States Patent No. 8,114,383 entitled "ABUSE-PROOFED DOSAGE FORM" ("the '383 patent"), including the right to sue and to recover for past infringement thereof. Purdue Pharma is an exclusive licensee of the '383 patent from Grünenthal, with the right to enforce the '383 patent. On February 14, 2012, Purdue Pharma submitted the paperwork to list the '383 patent in the FDA's Orange Book as covering 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg dosage strengths of the drug OxyContin®, which is the subject of approved NDA No. 022272. On June 26, 2012, Purdue Pharma submitted the paperwork to list the '383 patent in the FDA's Orange Book as covering 60 mg and 80 mg dosage strengths of the drug OxyContin®. A copy of the '383 patent is attached hereto as Exhibit A, which was duly and legally issued on February 14, 2012, naming Johannes Bartholomäus, Heinrich Kugelmann, and Elisabeth Arkenau-Marić as the inventors.

DEFENDANT'S ANDA

10. Upon information and belief, Actavis submitted ANDA No. 202434 to the FDA, under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), seeking approval to engage in the commercial manufacture, use, sale, offer for sale or importation of generic oxycodone hydrochloride extended release tablets ("proposed generic copies of OxyContin®"), 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg, based on the Reference Listed Drug ("RLD") OxyContin®, which is the subject of approved NDA No. 022272, before the expiration of the '383 patent.

11. Upon information and belief, Actavis's ANDA No. 202434 contains a "Paragraph IV" certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) alleging that the '383 patent, listed in the FDA's Orange Book as covering the drug OxyContin®, which is the subject of approved NDA No. 022272, is "invalid, unenforceable or will not be infringed by the commercial manufacture, use, importation, offer for sale or sale of [the proposed generic copies of OxyContin®]."

12. In a letter dated June 6, 2012 addressed to Plaintiffs and received by Purdue Pharma on June 6, 2012, Actavis provided "Notice" with respect to its proposed generic copies of OxyContin®, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg and the '383 patent under 21 U.S.C. § 355(j)(2)(B), and thereby demonstrated an actual and justiciable controversy.

FIRST CLAIM FOR RELIEF: PATENT INFRINGEMENT UNDER 35 U.S.C. § 271(e)(2) WITH RESPECT TO ACTAVIS'S PROPOSED GENERIC COPIES OF OXYCONTIN® 10 MG, 15 MG, 20 MG, 30 MG, AND 40 MG

13. Actavis's submission of its ANDA was an act of infringement of the '383 patent under the United States Patent Law, 35 U.S.C. § 271(e)(2)(A), with respect to Actavis's

proposed generic copies of OxyContin®, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg.

14. Upon information and belief, Actavis's proposed generic copies of OxyContin®, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg, are covered by one or more claims of the '383 patent.

15. Upon information and belief, Actavis's commercial manufacture, use, sale, and/or offer for sale of the proposed generic copies of OxyContin®, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg, would infringe, contribute to the infringement of, and/or induce the infringement of one or more claims of the '383 patent.

16. Upon information and belief, Actavis has been aware of the existence of the '383 patent, and has no reasonable basis for believing that its proposed generic copies of OxyContin®, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg, will not infringe the '383 patent, thus rendering the case "exceptional," as that term is used in 35 U.S.C. § 285.

17. The acts of infringement by Actavis set forth above will cause Plaintiffs irreparable harm for which they have no adequate remedy at law, and will continue unless enjoined by this Court.

SECOND CLAIM FOR RELIEF:
DECLARATORY JUDGMENT OF PATENT INFRINGEMENT WITH RESPECT TO ACTAVIS'S PROPOSED GENERIC COPIES OF OXYCONTIN® 60 MG AND 80 MG

18. Upon information and belief, once the FDA grants tentative approval of Actavis's ANDA, Actavis will undertake substantial activities directed toward engaging in infringement, contributory infringement, and active inducement of infringement of the '383 patent by making, using and undertaking substantial preparations for offering to sell, without authority from Plaintiffs, its proposed generic copies of OxyContin®, 60 mg and 80 mg, whose compositions are covered by one or more claims of the '383 patent.

19. Upon information and belief, Actavis has been aware of the existence of

the '383 patent but, once the FDA grants tentative approval of Actavis's ANDA, Actavis will nevertheless engage in substantial activities directed toward infringing, contributorily infringing, and actively inducing infringement of the '383 patent. These activities will be in total disregard for Plaintiffs' lawful rights under the '383 patent, thus rendering this case "exceptional" as that term is set forth in 35 U.S.C. § 285.

20. Once the FDA grants tentative approval of Actavis's ANDA, these substantial activities engaged in by Actavis directed toward infringement, contributory infringement, and active inducement of infringement as set forth above demonstrate the existence of an actual and justiciable controversy (*see* paragraph 12 above), and, if allowed to continue and progress, will inevitably constitute infringement, contributory infringement, and active inducement of infringement of the '383 patent, will cause Plaintiffs irreparable harm for which they have no adequate remedy at law, and will continue unless preliminarily and permanently enjoined by this Court.

WHEREFORE, Plaintiffs pray for judgment:

On the First Claim for Relief:

A. Adjudging that Actavis has infringed the '383 patent, and that the commercial sale, offer for sale, use, and/or manufacture of the proposed generic copies of OxyContin®, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg, described in ANDA No. 202434 would infringe, induce infringement of, and/or contribute to the infringement of the '383 patent;

B. Adjudging, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of ANDA No. 202434, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg, under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), to be a date not earlier than the date of expiration of the '383 patent plus any additional periods of exclusivity;

C. Preliminarily and permanently enjoining, pursuant to 35 U.S.C.

§§ 271(e)(4)(B) and 283 and Rule 65, Fed. R. Civ. P., Actavis, its officers, partners, agents, servants, employees, parents, subsidiaries, divisions, affiliate corporations, other related business entities and all other persons acting in concert, participation, or in privity with them, and their successors and assigns, from any commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of any drug product that infringes the '383 patent;

D. Declaring this an exceptional case and awarding Plaintiffs their attorneys' fees, as provided by 35 U.S.C. §§ 271(e)(4) and 285; and

E. Awarding Plaintiffs such other and further relief as this Court may deem just and proper.

On the Second Claim for Relief:

F. Declaring that the manufacture, use, and substantial preparations for offering for sale of Actavis's proposed generic copies of OxyContin®, 60 mg and 80 mg, if allowed to continue and progress, will constitute infringement, contributory infringement and active inducement of infringement of the '383 patent;

G. Preliminarily and permanently enjoining, pursuant to 35 U.S.C. § 283 and Rule 65, Fed. R. Civ. P., Actavis, its officers, partners, agents, servants, employees, parents, subsidiaries, divisions, affiliate corporations, other related business entities, and all other persons acting in concert, participation, or in privity with them, and their successors and assigns, from any commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of any drug product that infringes the '383 patent;

H. Declaring this an exceptional case and awarding Plaintiffs their attorneys' fees, as provided by 35 U.S.C. § 285; and

I. Awarding Plaintiffs such other and further relief as this Court may deem just and proper.

Dated: July 20, 2012

ROPES & GRAY LLP

Sona De
Pablo D. Hendler
1211 Avenue of the Americas
New York, NY 10036
(212) 596-9000
sona.de@ropesgray.com
pablo.hendler@ropesgray.com

Robert J. Goldman
1900 University Avenue, 6th Floor
East Palo Alto, CA 94303
(650) 617-4000
robert.goldman@ropesgray.com

Attorneys for Plaintiff
Purdue Pharma L.P.

Dated: July 20, 2012

WILK AUSLANDER LLP

Stephen D. Hoffman (SH 6089)
1515 Broadway, 43rd Floor
New York, NY 10036
(212) 981-2300
shoffman@wilkauslander.com

Attorneys for Plaintiff
Grünenthal GmbH

Of Counsel for Grünenthal GmbH:

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP

Basil J. Lewris
Joann M. Neth
Jennifer H. Roscetti
901 New York Avenue, N.W.
Washington, DC 20001
(202) 408-4000
bill.lewris@finnegan.com
joann.neth@finnegan.com
jennifer.roscetti@finnegan.com

Anthony C. Tridico
Avenue Louise 326, Box 37
Brussels, Belgium B-1050
011 32 2 646 03 53
anthony.tridico@finnegan.com

EXHIBIT A

US008114383B2

(12) United States Patent
Bartholomäus et al.

(10) Patent No.: US 8,114,383 B2
(45) Date of Patent: *Feb. 14, 2012

(54) **ABUSE-PROOFED DOSAGE FORM**

(75) Inventors: **Johannes Bartholomäus**, Aachen (DE); **Heinrich Kugelmann**, Aachen (DE); **Elisabeth Arkenau-Marić**, Köln (DE)

(73) Assignee: **Gruenenthal GmbH**, Aachen (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 325 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/718,112**

(22) Filed: **Nov. 20, 2003**

(65) **Prior Publication Data**

US 2005/0031546 A1 Feb. 10, 2005

(30) **Foreign Application Priority Data**

Aug. 6, 2003 (DE) 103 36 400

(51) **Int. Cl.**
A61K 49/00 (2006.01)

(52) **U.S. Cl.** **424/10.1**; 424/10.4

(58) **Field of Classification Search** 424/10.1
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,806,603	A		4/1974	Gaunt et al.
3,865,108	A		2/1975	Hartop
3,966,747	A		6/1976	Monkovic
3,980,766	A		9/1976	Shaw et al.
4,002,173	A		1/1977	Manning et al.
4,014,965	A		3/1977	Stube et al.
4,070,494	A		1/1978	Hoffmeister et al. 424/2
4,070,497	A		1/1978	Wismer
4,175,119	A	*	11/1979	Porter 424/475
4,207,893	A		6/1980	Michaels
4,262,017	A		4/1981	Kuipers
4,343,789	A		8/1982	Kawata et al.
4,353,887	A		10/1982	Hess
4,404,183	A		9/1983	Kawata et al.
4,427,681	A		1/1984	Manshi
4,462,941	A		7/1984	Lee
4,603,143	A		7/1986	Schmidt
4,612,008	A		9/1986	Wong et al. 604/892
4,629,621	A		12/1986	Snipes
4,690,822	A		9/1987	Uemura et al.
4,713,243	A		12/1987	Schiraldi et al.
4,744,976	A		5/1988	Snipes et al.
4,764,378	A		8/1988	Keith et al.
4,765,989	A		8/1988	Wong et al. 424/473
4,774,074	A		9/1988	Snipes
4,783,337	A		11/1988	Wong et al. 424/468
4,806,337	A		2/1989	Snipes et al.
RE33,093	E		10/1989	Schiraldi et al.
4,880,585	A		11/1989	Klimesch
4,892,778	A		1/1990	Theeuwes et al.
4,892,889	A		1/1990	Kirk
4,940,556	A		7/1990	MacFarlane
4,957,668	A		9/1990	Plackard
4,957,681	A		9/1990	Klimesch
4,960,814	A		10/1990	Wu
4,992,278	A		2/1991	Khanna
4,992,279	A		2/1991	Palmer
5,004,601	A		4/1991	Snipes
5,051,261	A		9/1991	McGinity et al.
5,169,645	A		12/1992	Shukla
5,198,226	A		3/1993	MacFarlane
5,200,197	A		4/1993	Wright et al.
5,211,892	A		5/1993	Gueret et al.
5,273,758	A		12/1993	Royce
5,350,741	A		9/1994	Takada
5,378,462	A		1/1995	Boedecker
5,427,798	A		6/1995	Ludwig
RE34,990	E		7/1995	Khanna
5,458,887	A		10/1995	Chen
5,460,826	A		10/1995	Merrill et al.
5,556,640	A		9/1996	Ito et al.
5,562,920	A		10/1996	Demmer et al.
5,601,842	A		2/1997	Bartholomaeus
5,620,697	A		4/1997	Tormala et al.
5,681,517	A		10/1997	Metzger
5,792,474	A		8/1998	Rauchfuss
5,801,201	A		9/1998	Graudums et al.
5,811,126	A		9/1998	Krishnamurthy
5,849,240	A	*	12/1998	Miller et al. 264/460
5,866,164	A	*	2/1999	Kuczynski et al. 424/472
5,916,584	A		6/1999	O'Donoghue
5,928,739	A		7/1999	Pophusen
5,945,125	A		8/1999	Kim
5,948,787	A		9/1999	Merrill et al.
5,968,925	A		10/1999	Knidlberger
6,009,390	A		12/1999	Gupta et al.
6,009,690	A		1/2000	Rosenberg
6,077,538	A		6/2000	Merrill
6,096,339	A		8/2000	Ayer et al.
6,117,453	A		9/2000	Seth et al.
6,133,241	A		10/2000	Bok
6,228,863	B1		5/2001	Palermo et al.
6,235,825	B1		5/2001	Yoshida
6,238,697	B1	*	5/2001	Kumar et al. 424/464
6,245,357	B1		6/2001	Edgren et al.
6,248,737	B1		6/2001	Buschmann et al.
6,261,599	B1		7/2001	Oshlack
6,306,438	B1		10/2001	Oshlack et al.

(Continued)

FOREIGN PATENT DOCUMENTS

AR	46994	12/2004

(Continued)

OTHER PUBLICATIONS

Zhang et al. (Pharm. Dev. Tech. 1999, 4, 241-250).*

(Continued)

Primary Examiner — Michael G Hartley
Assistant Examiner — Melissa Perreira
(74) *Attorney, Agent, or Firm* — Norris McLaughlin & Marcus, P.A.

(57) **ABSTRACT**

The present invention relates to an abuse-proofed, thermoformed dosage form containing, in addition to one or more active ingredients with abuse potential optionally together with physiologically acceptable auxiliary substances, at least one synthetic or natural polymer with a breaking strength of at least 500 N and to a process for the production thereof.

9 Claims, No Drawings

U.S. PATENT DOCUMENTS

6,309,668	B1	10/2001	Bastin et al.	424/472
6,340,475	B2	1/2002	Shell et al.	
6,344,535	B1	2/2002	Timmermann	
6,348,469	B1	2/2002	Seth	
6,375,963	B1	4/2002	Repka et al.	
6,399,100	B1	6/2002	Clancy et al.	
6,419,954	B1	7/2002	Chu	
6,436,441	B1	8/2002	Sako et al.	
6,461,644	B1	10/2002	Jackson	
6,488,962	B1	12/2002	Berner et al.	
6,488,963	B1	12/2002	McGinity et al.	
6,534,089	B1	3/2003	Ayer et al.	
6,547,997	B1	4/2003	Breitenbach et al.	
6,562,375	B1	5/2003	Sako et al.	
6,592,901	B2	7/2003	Durig	
6,635,280	B2	10/2003	Shell et al.	
6,699,503	B1	3/2004	Sako et al.	
6,723,340	B2	4/2004	Gusler et al.	
6,733,783	B2 *	5/2004	Oshlack et al.	424/473
6,753,009	B2	6/2004	Luber et al.	
6,821,588	B1	11/2004	Hammer	
7,141,250	B2	11/2006	Oshlack et al.	
7,176,251	B1	2/2007	Bastioli	
7,776,314	B2	8/2010	Bartholomäus et al.	
2001/0038852	A1	11/2001	Kolter	
2002/0012701	A1	1/2002	Kolter	
2002/0015730	A1	2/2002	Hoffmann	
2002/0051820	A1	5/2002	Shell et al.	
2002/0114838	A1	8/2002	Ayer et al.	
2002/0132359	A1	9/2002	Waterman	
2002/0187192	A1	12/2002	Joshi	
2003/0015814	A1	1/2003	Krull	
2003/0017532	A1	1/2003	Biswas	
2003/0021546	A1	1/2003	Sato	
2003/0031546	A1	2/2003	Araki	
2003/0044458	A1	3/2003	Wright, IV	
2003/0044464	A1	3/2003	Ziegler et al.	
2003/0064099	A1	4/2003	Oshlack et al.	424/465
2003/0068392	A1	4/2003	Sackler	424/760
2003/0091630	A1	5/2003	Louie-Helm et al.	
2003/0104052	A1	6/2003	Berner et al.	
2003/0118641	A1	6/2003	Maloney et al.	424/465
2003/0124185	A1	7/2003	Oshlack et al.	424/465
2003/0125347	A1	7/2003	Anderson et al.	
2003/0133985	A1	7/2003	Louie-Helm et al.	
2003/0152622	A1	8/2003	Louie-Helm et al.	
2003/0158242	A1	8/2003	Kugelmann	
2003/0175326	A1	9/2003	Thombre	
2003/0232895	A1	12/2003	Omidian	
2004/0010000	A1	1/2004	Ayer et al.	
2004/0011806	A1	1/2004	Luciano	
2004/0052844	A1	3/2004	Hsiao et al.	
2004/0081694	A1	4/2004	Oshlack	
2004/0091528	A1	5/2004	Rogers	
2004/0131671	A1	7/2004	Zhang	
2004/0156899	A1	8/2004	Louie-Helm et al.	
2004/0170567	A1 *	9/2004	Sackler	424/10.1
2004/0185105	A1	9/2004	Berner et al.	
2004/0213848	A1	10/2004	Li et al.	
2005/0015730	A1	1/2005	Gunturi et al.	
2005/0031546	A1	2/2005	Bartholomaus et al.	
2005/0058706	A1	3/2005	Bartholomaus	
2005/0063214	A1	3/2005	Takashima	
2005/0089475	A1	4/2005	Gruber	
2005/0095291	A1	5/2005	Oshlack et al.	
2005/0106249	A1	5/2005	Hwang et al.	
2005/0112067	A1	5/2005	Kumar et al.	
2005/0127555	A1	6/2005	Gusik	
2005/0152843	A1	7/2005	Bartholomaus	
2005/0186139	A1	8/2005	Bartholomaus	
2005/0191244	A1	9/2005	Bartholomaus	
2005/0214223	A1	9/2005	Bartholomaeus	
2005/0236741	A1	10/2005	Arkenau	
2005/0266084	A1	12/2005	Li et al.	
2006/0002859	A1	1/2006	Arkenau	
2006/0002860	A1	1/2006	Bartholomaus	
2006/0039864	A1	2/2006	Bartholomaus	
2006/0099250	A1	5/2006	Tian	
2006/0188447	A1	8/2006	Arkenau-Maric	
2006/0193782	A1	8/2006	Bartholomaus	
2006/0193914	A1	8/2006	Ashworth	
2006/0240110	A1	10/2006	Kiick et al.	
2007/0003616	A1	1/2007	Arkenau-Maric	
2007/0020188	A1	1/2007	Sackler	
2007/0020335	A1	1/2007	Chen et al.	
2007/0048228	A1	3/2007	Arkenau-Maric	
2007/0065365	A1	3/2007	Kugelmann	
2007/0092573	A1	4/2007	Joshi et al.	
2007/0183979	A1	8/2007	Arkenau-Maric	
2007/0183980	A1	8/2007	Arkenau-Maric	
2007/0190142	A1	8/2007	Breitenbach	
2007/0196396	A1	8/2007	Pilgaonkar et al.	
2007/0196481	A1	8/2007	Amidon	
2007/0264327	A1	11/2007	Kumar et al.	
2007/0269505	A1	11/2007	Flath et al.	
2008/0081290	A1	4/2008	Wada	
2008/0247959	A1	10/2008	Bartholomaus	
2008/0248113	A1	10/2008	Bartholomaus	
2008/0311049	A1	12/2008	Arkenau-Maric	
2008/0311187	A1	12/2008	Ashworth	
2008/0311197	A1	12/2008	Arkenau-Maric	
2008/0312264	A1	12/2008	Arkenau-Maric	
2008/0317854	A1	12/2008	Arkenau	
2009/0004267	A1	1/2009	Arkenau-Maric	
2009/0005408	A1	1/2009	Arkenau-Maric	
2009/0081290	A1	3/2009	McKenna	
2009/0202634	A1	8/2009	Jans	
2010/0015223	A1	1/2010	Cailly-Dufestel	
2010/0098758	A1	4/2010	Bartholomaus et al.	
2010/0151028	A1	6/2010	Ashworth et al.	
2010/0221322	A1	9/2010	Bartholomaus et al.	
2010/0260833	A1	10/2010	Bartholomaus et al.	
2011/0020451	A1	1/2011	Bartholomaus et al.	
2011/0038930	A1	2/2011	Barnscheid et al.	
2011/0082214	A1	4/2011	Faure et al.	

FOREIGN PATENT DOCUMENTS

AR	045353		10/2005
AR	049562		8/2006
AR	053304		5/2007
AR	054222		6/2007
AR	054328		6/2007
AU	2003237944		12/2003
AU	2003274071		5/2004
AU	2003278133		5/2004
AU	2003279317		5/2004
AU	2004264666		2/2005
AU	2004264667		2/2005
AU	2004308653		4/2005
AU	2005259476		1/2006
AU	2005259478		1/2006
AU	2006210145		8/2006
AU	2009207796		7/2009
AU	2009243681		11/2009
BR	P10413318		10/2006
BR	P10413361		10/2006
BR	P10513300		5/2008
BR	P10606145		2/2009
CA	2317747	A1	7/1999
CA	2352874	A1	6/2000
CA	250 2965	A1	5/2004
CA	2534925		2/2005
CA	2534932		2/2005
CA	2551231		7/2005
CA	2572352		1/2006
CA	2572352	A1	1/2006
CA	2572491		1/2006
CA	2595954		7/2006
CA	2595979		8/2006
CA	2713128		7/2009
CA	2723438		11/2009
CH	689109	A5	10/1998
CN	1980643		4/2005
CN	101010071		6/2005
CN	101022787		1/2006
CN	001863513		11/2006
CN	001863514		11/2006

CN	01917862		2/2007
CN	101027044		8/2007
CN	101111232		1/2008
CN	101175482		2/2008
DE	2530 563		1/1977
DE	2808505	A1	9/1978
DE	4309528		3/1993
DE	43 09 528		9/1994
DE	69400215	T2	10/1996
DE	19522899	C1	12/1996
DE	19753534		12/1997
DE	19800698		1/1998
DE	19822979		5/1998
DE	19753534	A1	6/1999
DE	19800689	C1	7/1999
DE	19800698	A1	7/1999
DE	19822979	A1	12/1999
DE	69229881	T2	12/1999
DE	0980894		2/2000
DE	19856147	A1	6/2000
DE	19940740	A1	3/2001
DE	19960494	A1	6/2001
DE	10036400	A1	6/2002
DE	19855440	A1	6/2002
DE	69429710	T2	8/2002
DE	10250083	A1	12/2003
DE	10250084	A1	5/2004
DE	10250087	A1	5/2004
DE	10250088		5/2004
DE	10336400	A1	3/2005
DE	102004019916		11/2005
DE	102004020220		11/2005
DE	10 2004 032049	A1	1/2006
DE	10 2004 032051	A1	1/2006
DE	10 2004 032103	A1	1/2006
DE	10 2005 005446	A1	8/2006
DE	10 2005 005449	A1	8/2006
DE	102007011485		9/2008
DK	1658055		7/2007
DK	1658054		10/2007
DK	1515702		1/2009
EC	SP066345		8/2006
EP	0 008 131		2/1980
EP	0043254	A1	1/1982
EP	0177893	A2	4/1986
EP	0 216 453		4/1987
EP	0 226 061		6/1987
EP	0 228 417		7/1987
EP	0229652	A2	7/1987
EP	0 232 877		8/1987
EP	0240906	A2	10/1987
EP	0261616	A2	3/1988
EP	0270954	A1	6/1988
EP	0 277 289		8/1988
EP	0 293 066		11/1988
EP	0 328 775		8/1989
EP	0477135	A1	3/1992
EP	0544144	A1	6/1993
EP	0 583 726		2/1994
EP	0 598 606		5/1994
EP	0636370	A1	2/1995
EP	0641195	A1	3/1995
EP	0647448	A1	4/1995
EP	0682945	A2	5/1995
EP	0 661 045		7/1995
EP	0661045	A1	7/1995
EP	0675710	A1	10/1995
EP	0693475		1/1996
EP	0693475	A1	1/1996
EP	0820693	A1	1/1996
EP	0 696 598		2/1996
EP	0756480	A1	2/1997
EP	0760654	A1	3/1997
EP	0780369		6/1997
EP	0780369	A1	6/1997
EP	0785775	A1	7/1997
EP	0809488	A1	12/1997
EP	0820698		1/1998
EP	0820698	A1	1/1998
EP	0857062	A2	8/1998
EP	0864324	A1	9/1998
EP	0864326	A2	9/1998
EP	0 980 894	A1	9/1999
EP	0988106	A1	3/2000
EP	1014941	A1	7/2000
EP	1070504	A1	1/2001
EP	1127871	A1	8/2001
EP	1138321	A2	10/2001
EP	1166776	A2	1/2002
EP	1251120	A1	10/2002
EP	1293127	A2	3/2003
EP	1293196	A2	3/2003
EP	1250045	B1	9/2003
EP	1658055		2/2005
EP	1515702		3/2005
EP	1527775	A1	4/2005
EP	1558221	A1	8/2005
EP	1558257		8/2005
EP	1560585		8/2005
EP	1658054		5/2006
EP	1740161		1/2007
EP	1765303		3/2007
EP	1786403		5/2007
EP	1558221	B1	6/2007
EP	1845955		10/2007
EP	1845956		10/2007
EP	1 859 789		11/2007
EP	1897545	A1	12/2008
EP	2131830		12/2009
EP	2249811		11/2010
EP	2273983		1/2011
ES	2336571		12/2004
ES	2260042	T3	11/2006
ES	2285497		11/2007
ES	2288621		1/2008
ES	2289542		2/2008
ES	2315505		4/2009
GB	1147210	A	4/1969
GB	2057878	A	4/1981
HR	P20070272		6/2007
HR	20070456		11/2007
JP	3-0501737	A	4/1991
JP	8 505076		6/1996
JP	8-505076	A	6/1996
JP	2002-275175	A	9/2002
JP	2005534664		11/2005
KR	1020060069832		6/2006
KR	20070039041		4/2007
KR	20070111510		11/2007
KR	20100111303		10/2010
KR	20110016921		2/2011
MX	2007000008		3/2007
MX	2007000009		3/2007
MX	2007009393		8/2007
MX	2010008138		8/2010
MX	2010012039		11/2010
NO	20061054		3/2006
NO	20070578		1/2007
NO	20074412		11/2007
PT	1699440		12/2004
PT	1658054		5/2006
PT	1658055		7/2007
PT	1515702		12/2008
RU	2131244	C1	6/1999
RU	2354357		12/2007
RU	2007103712		9/2008
RU	2007103707		11/2008
RU	2007132975		4/2009
SI	1515702		4/2009
SI	1699440		11/2009
WO	89/05624	A1	6/1989
WO	90 03776		4/1990
WO	9003776	A1	4/1990
WO	93 06723		4/1993
WO	93 10758	A1	6/1993
WO	93 11749		6/1993
WO	94 06414		3/1994
WO	94 08567	A1	4/1994

WO	95/17174	A1		6/1995
WO	95 22319	A1		8/1995
WO	WO 95/20947			8/1995
WO	95 30422			11/1995
WO	96 00066			1/1996
WO	96/03979	A1		2/1996
WO	9614058	A1		5/1996
WO	9733566			9/1997
WO	9820073			5/1998
WO	WO 98/20073			5/1998
WO	98 28698	A1		7/1998
WO	98/35655	A2		8/1998
WO	99/12864	A1		3/1999
WO	99 32120	A1		7/1999
WO	99/48481	A1		9/1999
WO	9944591	A1		9/1999
WO	WO/00/33835		*	6/2000
WO	WO0033835		*	6/2000
WO	0040205			7/2000
WO	01/12230	A1		2/2001
WO	0108661	A2		2/2001
WO	0115667	A1		3/2001
WO	01/52651	A2		7/2001
WO	01/97783	A1		12/2001
WO	02/26061	A1		4/2002
WO	02/26262	A2		4/2002
WO	02 26928			4/2002
WO	02/088217	A1		11/2002
WO	03 06723	A1		1/2003
WO	03 013476	A1		2/2003
WO	03/013479	A1		2/2003
WO	WO 03/015531			2/2003
WO	WO 03/015531	A2		2/2003
WO	03 024430			3/2003
WO	03/026624	A1		4/2003
WO	03 026743	A2		4/2003
WO	03/026743	A2		4/2003
WO	03 028698	A2		4/2003
WO	03/028990	A1		4/2003
WO	03/031546	A1		4/2003
WO	03 035029			5/2003
WO	03/035177	A2		5/2003
WO	03035029	A1		5/2003
WO	03035053	A1		5/2003
WO	03035054	A1		5/2003
WO	03053417	A2		7/2003
WO	03/068392	A1		8/2003
WO	03/092648	A1		11/2003
WO	03094812	A1		11/2003
WO	03 105808			12/2003
WO	2004/004693	A1		1/2004
WO	2004/043967	A1		2/2004
WO	2004 026263	A2		4/2004
WO	WO/2004/026262			4/2004
WO	WO 2004026262	A2	*	4/2004
WO	2004037230	A1		5/2004
WO	2004037259	A1		5/2004
WO	2004037260	A1		5/2004
WO	2004/066910	A2		8/2004
WO	2004/084869	A1		10/2004
WO	2004/093801	A2		11/2004
WO	2004/100894	A2		11/2004
WO	2004093819	A2		11/2004
WO	2005 016313			2/2005
WO	2005 016314			2/2005
WO	2005016314	A1		2/2005
WO	2005/032524	A2		4/2005
WO	2005/065646	A2		4/2005
WO	2005 041968			5/2005
WO	2005/053656	A1		6/2005
WO	2005/055981	A2		6/2005
WO	2005 063214			7/2005
WO	2005/066183	A1		7/2005
WO	2005063214	A1		7/2005
WO	2005 102286			11/2005
WO	2005102286	A1		11/2005
WO	2006 002883			1/2006
WO	2006 002884			1/2006
WO	2006002884			1/2006
WO	2006002886	A1		1/2006
WO	2005102294			5/2006
WO	2006 082097			8/2006
WO	2006 082099			8/2006
WO	2007/005716	A2		1/2007
WO	2007 008752			1/2007
WO	2007 048233			5/2007
WO	2007 053698			5/2007
WO	2007/085024	A2		7/2007
WO	2008/086804	A2		7/2008
WO	2008/107149	A2		9/2008
WO	2008107149			9/2008
WO	2008/148798	A2		12/2008
WO	2009003776	A1		1/2009
WO	2009/092601	A1		7/2009
WO	2009092601			7/2009
WO	2009/135680	A1		11/2009
WO	2009135680			11/2009
WO	2011009602			1/2011
WO	2011009603			1/2011
WO	2011009604			1/2011

OTHER PUBLICATIONS

Maggi et al. (Biomaterials 2002, 23, 1113-1119).*

DOW Technical Data, POLYOXTIM WSR, Feb. 2003.*

DeJong (Pharmaceutisch Weekblad Scientific Edition 1987, p. 24-28).*

Observations by Third Parties Pursuant to Art 115 EPC, dated Feb. 2, 2009.

Letter of James W. McGinity, with attached experimental report, dated Jan. 26, 2009.

V.K. Thoma et al., "Bestimmung der In-vitro-Freigabe von schwach basischen Wirkstoffen aus Retardarzneiformen," Pharm. Ind. 51, Nr. 3 (1989).

F. E. Bailey et al., "Some Properties of Poly(ethylene oxide) in Aqueous Solution," Journal of Applied Polymer Science, vol. 1, Issue No. 1, pp. 56-62 (1959).

A. Apicella et al., "Poly(ethylene oxide) (PEO) and different molecular weight PEO blends monolithic devices for drug release," Biomaterials 1993, vol. 14, No. 2, pp. 83-90.

S. Janicki et al., "Slow-Release Microballs: Method of Preparation," Acta Pharm. Technol. 33(3) 154-155 (1987).

R. Mank et al., "Darstellung wirkstoffhaltiger Extrusionsformlinge auf der Basis von Thermoplasten," Pharmazie 45 (1990), H. 8; pp. 592-593.

R. Mank et al., "Darstellung wirkstoffhaltiger Extrusionsformlinge auf der Basis von Thermoplasten," Pharmazie 44 (1989) H. 11; pp. 773-776.

P. Shivanand et al., "Factors Affecting Release of KCl from Melt Extruded Polyethylene Disks," Pharmaceutical Research, Official Journal of the American Association of Pharmaceutical Scientists; Oct. 1991, vol. 8, No. 10.

L. Yang et al., "Characterization of Compressibility and Compatibility of Poly(ethylene oxide) Polymers for Modified Release Application by Compaction Simulator," Journal of Pharmaceutical Sciences, vol. 85, No. 10, Oct. 1996.

F. Zhang et al., "Properties of Sustained-Release Tablets Prepared by Hot-Melt Extrusion," Pharmaceutical Development and Technology, 4(2), 241-250 (1999) pp. 241-250.

M.M. Crowley et al., "Stability of polyethylene oxide in matrix tablets prepared by hot-melt extrusion," Biomaterials 23 (2002) 4241-4248.

M. Efentakis et al., "Evaluation of High Molecular Weight Poly(Oxyethylene) (Polyox) Polymer: Studies of Flow Properties and Release Rates of Furosemide and Captopril from Controlled-Release Hard Gelatin Capsules," Pharmaceutical Development and Technology, 5(3), 339-346 (2000).

N. Follonier et al., "Various ways of modulating the release of diltiazem hydrochloride from hot-melt extruded sustained release pellets prepared using polymeric materials," Journal of Controlled Release 36 (1995) 243-250.

N.B. Graham, "Poly(Ethylene Glycol) Gels and Drug Delivery," Poly(Ethylene Glycol) Chemistry: Biotechnical and Biomedical Applications, Chapter 17, 1992.

C. D. Hanning et al., "The Morphine Hydrogel Suppository," British Journal of Anaesthesia, 1988, 61, 221-227.
Kim et al., "Preparation and Evaluation of Eudragit Gels V. Rectal Gel Preparations for Sustained Release and Avoidance of First-Pass Metabolism of Lidocaine," Chem. Pharm. Bull. 40(10) 2800-2804 (1992).
Cherng-Ju Kim, "Drug Release from Compressed Hydrophilic POLYOX-WSR Tablets," Journal of Pharmaceutical Sciences, vol. 84, No. 3, Mar. 1995.
S.L. Madorsky et al., "Thermal Degradation of Polyethylene Oxide and Polypropylene Oxide," Journal of Polymer Science, vol. XXXVI, pp. 183-194 (1959).
A. Moroni et al., "Application of Poly(Oxyethylene) Homopolymers in Sustained Release Solid Formulations," Drug Development and Industrial Pharmacy, 21(12), 1411-1428 (1995).
N. Ohnishi et al., "Effect of the Molecular Weight of Polyethylene Glycol on the Bioavailability of Indomethacin Sustained-Release Suppositories Prepared with Solid Dispersions," Chem. Pharm. Bull., 35 (8) 3511-3515 (1987).
T. Ozeki et al., "Control of medicine release from solid dispersion composed of the poly(ethylene oxide)-carboxyvinylpolymer interpolymer complex by varying molecular weight of poly(ethylene oxide)," Journal of Controlled Release 58 (1999) 87-95.
Pharmaceutical Research, Official Journal of the American Association of Pharmaceutical Scientists, Sep. 1989 (Supplement), vol. 6, No. 9, 6.S-98.
Pharmaceutical Research, Official Journal of the American Association of Pharmaceutical Scientists, Oct. 1991 (Supplement), Vo. 8, No. 10, 8.S-192.
W. Prapaitrakul et al., "Release of Chlorpheniramine Maleate from Fatty Acid Ester Matrix Disks Prepared by Melt-extrusion," J. Pharm. Pharmacol. 1991, 43: 377-381.
S. Radko et al., "Molecular sieving by polymer solutions: dependence on particle and polymer size, independence of polymer entanglement," Applied and Theoretical Electrophoresis (1995), 5, 79-88.
J. Scheirs et al., "Characterizing the solid-state thermal oxidation of poly(ethylene oxide) powder," Polymer, 1991, vol. 32, No. 11.
O.L. Sprockel et al., "Permeability of Cellolose Polymers: Water Vapour Transmission Rates," J. Pharm. Pharmacol. 1990, 42: 152-157.
J.L. Stringer et al., "Diffusion of small molecular weight drugs in radiation-crosslinked poly(ethylene oxide) hydrogels," Journal of Controlled Release 42 (1996) 195-202.
E. G. Rippie et al., "Regulation of Dissolution Rate by Pellet Geometry," Journal of Pharmaceutical Sciences, Vo. 58, No. 4, Apr. 1969, pp. 428-431.
M. Adel El-Egakey et al., "Hot extruded dosage forms Part I," Pharmaceutica Acta Helvetiae, vol. 46, Mar. 19, 1970.
Remington's Pharmaceutical Sciences 17th ed., Mack Publishing Co., (1985) 1418.
M.S. Mesiha et al., "A Screening Study of Lubricants in Wet Powder Masses Suitable for Extrusion Spheronization," Drug Development and Industrial Pharmacy, 19(8), 943-959 (1993).
N. Follonier et al., "Evaluation of Hot-Melt Extrusion as a New Technique for the Production of Polymer-Based Pellets for Sustained Release Capsules Containing High Loadings of Freely Soluble Drugs," Drug Development and Industrial Pharmacy, 20(8), 1323-1339 (1994).
Remington's Pharmaceutical Sciences, Authur Asol editor, pp. 1553-1593, Chapter 89, 1980.
Inert Gas from Wikipedia (Dec. 2009).
Coppens et al; "Hypromellose, Ethylcellulose, and Polyethylene Oxide Use in Hot Melt Extrusion"; Pharmaceutical Technology, 62-70, Jan. 2005.
Caraballo et al., "Percolation Thresholds in Ultrasound Compacted Tablets", Journal of Controlled Release, vol. 69, pp. 345-355, (2000).
El-Sherbiny et al., "Preparation Characterization, Swelling and in Vitro Drug Release Behaviour of Poly[N-acryloylglycine-chitosan] Interpolymeric pH and Thermally-responsice Hydrogels", European Polymer Journal, vol. 41, pp. 2584-2591 (2005).
Griffith R., "Tablet Crushing and the Law: The Implications for Nursing", Drug Administration, vol. 19, No. 1, p. 41-42 (2003).
Levina et al., "The Effect of Ultrasonic Vibration on the Compaction Characteristic of Paracetamol", Journal of Pharmaceutical Sciences, vol. 89, No. 6, pp. 705-723, Jun. 2000.
Levina et al., "The Effecto of Ultrasonic Vibration on the Compaction Characteristic of Ibuprofen", Drug Development and Industrial Pharmacy, vol. 28, No. 5, pp. 495-514 (2002).
Miller, et al., "To Crush or Not to Be Crush", Nursing, p. 50-52, Feb. 2000.
Mitchell J.E., "Oral Dosage Forms That Should Not Be Crushed: 2000 Update", Special Resource, vol. 35, No. 5, pp. 553-557, (2000).
Proeschel et al., "Task-Dependence of Activity/Bite-force Relations and its Impact on Estimation of Chewing Force from EMG", J. Dent. Res., vol. 81, No. 7, pp. 464-468 (2002).
Jan. 6, 2011 Letter from Dr. Rick Matos, Ph.D.
Seach result conducted on http://www.unitconversion.org/force/newtons-to-kiloponds-conversion.html on Jul. 5, 2011.
Katz et al., Clin. J. Pain, 23(8): 648-660 (2007).
Arnold, "Teen Abuse of Painkiller OxyContin on the Rise," www.npr.org, Dec. 19, 2005.
Baum et al., Public Health Reports, 102(4): 426-429 (1987).
Purdue News, "Purdue Pharma Provides Update on Development of New Abuse-Resistant Pain Medications; FDA Cites Patient Needs As First Priority; New Drug Application Delayed," www.headaches.about.com, Jun. 18, 2002.
Strang, British Med. J., 302: 969 (1991).
Tompkins et al., Psychopharma., 210: 471-480 (2010).
Waters et al., Am. J. Psychiatry, 164(1): pp. 173-174 (2007).
Tablet, www.docstoc.com (2011).
Dachille, F. et al., "High-Pressure Phase Transformation in Laboratory Mechanical Mixers and Mortars", 1906., Nature, 186, pp. 1-2 (abstract).
Yarbrough et al., Letters to Nature 322, 347-349 (Jul. 24, 1986) "Extraodinary effects of mortar-and-pestle grinding on microstructure of sintered alumina gel".
Braun, et al. Angel Orthodontist, 6(5) pp. 373-377, 1995.
Dow Excipients Chem. of Poly. Water Soluble Resin 2004.
Davis et al., European Journal of Pharmaceutics and Biopharmaceutics, 67, 2007, pp. 268-276.
Fell, et al. Journal of Pharmaceutical Sciences, vol. 59, No. 5, May 1970, pp. 688-691.
Lockhart et al. "Packaging of Pharmaceuticals and Health Care Products"; Blackie Academic & Professional; First Edition 1996.
Manthena et al., Amer J Drug Deliv. 2004: 2(1): 43-57.
Summers et al; Journal of Pharmaceutical Sciences, vol. 66, No. 8, Aug. 1977, pp. 1172-1175.
Tipler et al. Physics for Scientists and Engineers, 6th Edition, pp. 234-235, 2003.
US Pharmacopoeia, Chapter 1217, Aug. 1, 2008.
Waltimo et al. A novel bite force recorder and maximal isometric bite force values for healthy young adults. Scand J Dent Res. 1993, vol. 101, pp. 171-175.
Waltimo et al. Maximal bite force and its association with signs and symptoms of crandiomandibular disorders in young Finnish non-patients. Acta Odonol. Scand. 1995, vol. 53, pp. 254-258.
Conversion of 18.8 kiloponds to newtons, http://www.unitconversion.org/force/newtons-to-kiloponds-conversion.html on Jul. 5, 2011.
Bauer, Coated Pharmaceutical Dosage Forms, CRC Press, 1998, pp. 1-10.
Dachille, T., et al. "High-pressure phase transformation in laboratory mechanical mixers and mortars", 1960, Nature, 186, pp. 1-2 (abstract).
Maggi, L. et al., "High molecular weight polyethylene oxides (PE0s) as an alternative to HPMC in controlled release dosage form", 2000, International Journal of Pharmaceutics, 195 pp, 229-238.
Maggi, "Therapeutic Potential of Capsaicin-like Molecules: Studies in Animals and Humans", Life Sciences, vol. 51, pp. 1777-1781, (1992).
2.9 Methoden der pharmazeutischen Technologie, pp. 143-144, 1997 (English Translation included).
Handbuch der Kunststoff-Extrusionstechnik , "Grundlagen", Chapter 1.2 "Klassifizierung von Extrudern", pp. 3-7, 1989, (English Translation included).

Freed et al. pH control of nucleophilic/electrophilic oxidation. International Journal of Pharmaceutics. 2008, vol. 357, pp. 180-188.
Waterman et al. Stabilization of Pharmaceuticals to Oxidative Degradation. Pharmaceutical Development and Technology. 2002, vol. 7, No. 1, pp. 1-32.
J. Stafford, "Überzogene feste Formen", H. Sucker, Georg Thieme Verlag 1991, pp. 347-368.
"Pharmaceutical technical procedures", European Pharmacopofia, 1997, p. 135.
Granulierung hydrophober Wirkstoffe im Planetwalzenextruder 2003.
Pharmazeutische Biologie Drogen und ihre Inhaltsstoffe, Professor Dr. Hildebert Wagner, Munchen, 1982, pp. 82-92.
Coated Pharmaceutical Dosage Forms, K.H. Bauer, et al., CRC Press, 1998, pp. 1-10.

* cited by examiner

ABUSE-PROOFED DOSAGE FORM

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to an abuse-proofed, thermoformed dosage form containing, in addition to one or more active ingredients with abuse potential (A) optionally together with physiologically acceptable auxiliary substances (B), at least one synthetic or natural polymer (C) and optionally at least one wax (D), wherein component (C) exhibits a breaking strength of at least 500 N, and to a process for the production of the dosage form according to the invention.

2. Brief Description of Related Developments

Many pharmaceutical active ingredients, in addition to having excellent activity in their appropriate application, also have abuse potential, i.e. they can be used by an abuser to bring about effects other than those intended. Opiates, for example, which are highly active in combating severe to very severe pain, are frequently used by abusers to induce a state of narcosis or euphoria.

In order to make abuse possible, the corresponding dosage forms, such as tablets or capsules are comminuted, for example ground in a mortar, by the abuser, the active ingredient is extracted from the resultant powder using a preferably aqueous liquid and the resultant solution, optionally after being filtered through cotton wool or cellulose wadding, is administered parenterally, in particular intravenously. An additional phenomenon of this kind of administration, in comparison with abusive oral administration, is a further accelerated increase in active ingredient levels giving the abuser the desired effect, namely the "kick" or "rush". This kick is also obtained if the powdered dosage form is administered nasally, i.e. is sniffed. Since controlled-release dosage forms containing active ingredients with abuse potential do not give rise to the kick desired by the abuser when taken orally even in abusively high quantities, such dosage forms are also comminuted and extracted in order to be abused.

U.S. Pat. No. 4,070,494 proposed adding a swellable agent to the dosage form in order to prevent abuse. When water is added to extract the active ingredient, this agent swells and ensures that the filtrate separated from the gel contains only a small quantity of active ingredient.

The multilayer tablet disclosed in WO 95/20947 is based on a similar approach to preventing parenteral abuse, said tablet containing the active ingredient with abuse potential and at least one gel former, each in different layers.

WO 03/015531 A2 discloses another approach to preventing parenteral abuse. A dosage form containing an analgesic opioid and a dye as an aversive agent is described therein. The colour released by tampering with the dosage form is intended to discourage the abuser from using the dosage form which has been tampered with.

Another known option for complicating abuse involves adding antagonists to the active ingredients to the dosage form, for example naloxone or naltexone in the case of opiates, or compounds which cause a physiological defence response, such as for example Radix ipecacuanha=ipecac root.

SUMMARY OF THE INVENTION

However, since in most cases of abuse it is still necessary to pulverise the dosage form comprising an active ingredient suitable for abuse, it was the object of the present invention to complicate or prevent the pulverisation preceding abuse of the dosage form comprising the agents conventionally available for potential abuse and accordingly to provide a dosage form for active ingredients with abuse potential which ensures the desired therapeutic effect when correctly administered, but from which the active ingredients cannot be converted into a form suitable for abuse simply by pulverisation.

Said object has been achieved by the provision of the abuse-proofed, thermoformed dosage form according to the invention which contains, in addition to one or more active ingredients with abuse potential (A), at least one synthetic or natural polymer (C) and optionally at least one wax (D), wherein component (C) exhibits a breaking strength of at least 500 N.

The use of polymers having the stated minimum breaking strength, preferably in quantities such that the dosage form also exhibits such a minimum breaking strength, means that pulverisation of the dosage form is considerably more difficult using conventional means, so considerably complicating or preventing the subsequent abuse.

If comminution is inadequate, parenteral, in particular intravenous, administration cannot be performed safely or extraction of the active ingredient therefrom takes too long for the abuser or there is no "kick" when taken orally, as release is not spontaneous.

According to the invention, comminution is taken to mean pulverisation of the dosage form with conventional means which are available to an abuser, such as for example a mortar and pestle, a hammer, a mallet or other usual means for pulverisation by application of force.

The dosage form according to the invention is thus suitable for preventing parenteral, nasal and/or oral abuse of pharmaceutical active ingredients with abuse potential.

Pharmaceutical active ingredients with abuse potential are known to the person skilled in the art, as are the quantities thereof to be used and processes for the production thereof, and may be present in the dosage form according to the invention as such, in the form of the corresponding derivatives thereof, in particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof, as racemates or stereoisomers. The dosage form according to the invention is also suitable for the administration of several active ingredients. It is preferably used to administer a specific active ingredient.

The dosage form according to the invention is in particular suitable for preventing abuse of a pharmaceutical active ingredient selected from the group consisting of opiates, opioids, tranquillisers, preferably benzodiazepines, barbiturates, stimulants and other narcotics.

The dosage form according to the invention is very particularly suitable for preventing abuse of an opiate, opioid, tranquilliser or another narcotic selected from the group consisting of N-{1-[2-(4-ethyl-5-oxo-2-tetrazolin-1-yl)ethyl]-4-methoxymethyl-4-piperidyl}propionanilide (alfentanil), 5,5-diallylbarbituric acid (allobarbital), allylprodine, alphaprodine, 8-chloro-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]-benzodiazepine (alprazolam), 2-diethylaminopropiophenone (amfepramone), (±)-α-methyl-phenethylamine (amphetamine), 2-α-methylphenethylamino)-2-phenylacetonitrile (amphetaminil), 5-ethyl-5-isopentylbarbituric acid (amobarbital), anileridine, apocodeine, 5,5-diethylbarbituric acid (barbital), benzylmorphine, bezitramide, 7-bromo-5-(2-pyridyl)-1H-1,4-benzodiazepine-2(3H)-one (bromazepam), 2-bromo-4-(2-chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo-[4,3-a][1,4]diazepine (brotizolam), 17-cyclopropylmethyl-4,5α-epoxy-7α[(S)-1-hydroxy-1,2,2-trimethyl-propyl]-6-

methoxy-6,14-endo-ethanomorphinane-3-ol (buprenorphine), 5-butyl-5-ethylbarbituric acid (butobarbital), butorphanol, (7-chloro-1,3-dihydro-1-methyl-2-oxo-5-phenyl-2H-1,4-benzodiazepine-3-yl)-dimethylcarbamate (camazepam), (1S,2S)-2-amino-1-phenyl-1-propanol (cathine/D-norpseudoephedrine), 7-chloro-N-methyl-5-phenyl-3H-1,4-benzodiazepine-2-ylamine-4-oxide (chlorodiazepoxide), 7-chloro-1-methyl-5-phenyl-1H-1,5-benzodiazepine-2,4(3H,5H)-dione (clobazam), 5-(2-chlorophenyl)-7-nitro-1H-1,4-benzodiazepine-2(3H)-one (clonazepam), clonitazene, 7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepine-3-carboxylic acid (clorazepate), 5-(2-chlorophenyl)-7-ethyl-1-methyl-1H-thieno[2,3-e][1,4]diazepine-2(3H)-one (clotiazepam), 10-chloro-11b-(2-chlorophenyl)-2,3,7,11b-tetrahydrooxazolo[3,2-d][1,4] benzodiazepine-6(5H)-one (cloxazolam), (−)-methyl-[3β-benzoyloxy-2β(1α(H,5αH)-tropancarboxylate] (cocaine), 4,5α-epoxy-3-methoxy-17-methyl-7-morphinene-6α-ol (codeine), 5-(1-cyclohexenyl)-5-ethylbarbituric acid (cyclobarbital), cyclorphan, cyprenorphine, 7-chloro-5-(2-chlorophenyl)-1H-1,4-benzodiazepine-2(3H)-one (delorazepam), desomorphine, dextromoramide, (+)-(1-benzyl-3-dimethylamino-2-methyl-1-phenylpropyl)propionate (dextropropoxyphen), dezocine, diampromide, diamorphone, 7-chloro-1-methyl-5-phenyl-1H-1,4-benzodiazepine-2(3H)-one (diazepam), 4,5α-epoxy-3-methoxy-17-methyl-6α-morphinanol (dihydrocodeine), 4,5α-epoxy-17-methyl-3,6α-morphinandiol (dihydromorphine), dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, (6aR,10aR)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromene-1-ol (dronabinol), eptazocine, 8-chloro-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine (estazolam), ethoheptazine, ethylmethylthiambutene, ethyl [7-chloro-5-(2-fluorophenyl)-2,3-dihydro-2-oxo-1H-1,4-benzodiazepine-3-carboxylate](ethyl loflazepate), 4,5α-epoxy-3-ethoxy-17-methyl-7-morphinene-6α-ol (ethylmorphine), etonitazene, 4,5α-epoxy-7α-(1-hydroxy-1-methylbutyl)-6-methoxy-17-methyl-6,14-endo-etheno-morphinan-3-ol (etorphine), N-ethyl-3-phenyl-8,9,10-trinorbornan-2-ylamine (fencamfamine), 7-[2-(1-methyl-phenethylamino)ethyl]-theophylline) (fenethylline), 3-(α-methylphenethylamino)propionitrile (fenproporex), N-(1-phenethyl-4-piperidyl) propionanilide (fentanyl), 7-chloro-5-(2-fluorophenyl)-1-methyl-1H-1,4-benzodiazepine-2(3H)-one (fludiazepam), 5-(2-fluorophenyl)-1-methyl-7-nitro-1H-1,4-benzodiazepine-2(3H)-one (flunitrazepam), 7-chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1H-1,4-benzodiazepine-2(3H)-one (flurazepam), 7-chloro-5-phenyl-1-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2(3H)-one (halazepam), 10-bromo-11b-(2-fluorophenyl)-2,3,7,11b-tetrahydro[1,3]oxazolyl[3,2-d][1,4]benzodiazepine-6(5H)-one (haloxazolam), heroin, 4,5α-epoxy-3-methoxy-17-methyl-6-morphinanone (hydrocodone), 4,5α-epoxy-3-hydroxy-17-methyl-6-morphinanone (hydromorphone), hydroxypethidine, isomethadone, hydroxymethyl morphinane, 11-chloro-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4H-[1,3]oxazino [3,2-d][1,4]benzodiazepine-4,7(6H)-dione (ketazolam), 1-[4-(3-hydroxyphenyl)-1-methyl-4-piperidyl]-1-propanone (ketobemidone), (3S,6S)-6-dimethylamino-4,4-diphenyl-heptan-3-yl acetate (levacetylmethadol (LAAM)), (−)-6-dimethyl-amino-4,4-diphenol-3-heptanone (levomethadone), (−)-17-methyl-3-morphinanol (levorphanol), levophenacylmorphane, lofentanil, 6-(2-chlorophenyl)-2-(4-methyl-1-piperazinylmethylene)-8-nitro-2H-imidazo[1,2-a] [1,4]-benzodiazepine-1(4H)-one (loprazolam), 7-chloro-5-(2-chlorophenyl)-3-hydroxy-1H-1,4-benzodiazepine-2(3H)-

one (lorazepam), 7-chloro-5-(2-chlorophenyl)-3-hydroxy-1-methyl-1H-1,4-benzodiazepine-2(3H)-one (lormetazepam), 5-(4-chlorophenyl)-2,5-dihydro-3H-imidazo[2,1-a]isoindol-5-ol (mazindol), 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepine (medazepam), N-(3-chloropropyl)-α-methylphenethylamine (mefenorex), meperidine, 2-methyl-2-propyltrimethylene dicarbamate (meprobamate), meptazinol, metazocine, methylmorphine, N,α-dimethylphenethylamine (methamphetamine), (±)-6-dimethylamino-4,4-diphenyl-3-heptanone (methadone), 2-methyl-3-o-tolyl-4(3H)-quinazolinone (methaqualone), methyl [2-phenyl-2-(2-piperidyl)acetate](methylphenidate), 5-ethyl-1-methyl-5-phenylbarbituric acid (methylphenobarbital), 3,3-diethyl-5-methyl-2,4-piperidinedione (methyprylon), metopon, 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine (midazolam), 2-(benzhydrylsulfinyl)-acetamide (modafinil), 4,5α-epoxy-17-methyl-7-morphinen-3,6α-diol (morphine), myrophine, (±)-trans-3-(1,1-dimethylheptyl)-7,8,10,10α-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyrane-9 (6αH)-one (nabilone), nalbuphine, nalorphine, narceine, nicomorphine, 1-methyl-7-nitro-5-phenyl-1H-1,4-benzodiazepine-2(3H)-one (nimetazepam), 7-nitro-5-phenyl-1H-1,4-benzodiazepine-2(3H)-one (nitrazepam), 7-chloro-5-phenyl-1H-1,4-benzodiazepine-2(3H)-one (nordazepam), norlevorphanol, 6-dimethylamino-4,4-diphenyl-3-hexanone (normethadone), normorphine, norpipanone, the exudation of plants belonging to the species *Papaver somniferum* (opium), 7-chloro-3-hydroxy-5-phenyl-1H-1,4-benzodiazepine-2 (3H)-one (oxazepam), (cis-trans)-10-chloro-2,3,7,11b-tetrahydro-2-methyl-11b-phenyloxazolo[3,2-d][1,4]benzodiazepine-6-(5H)-one (oxazolam), 4,5α-epoxy-14-hydroxy-3-methoxy-17-methyl-6-morphinanone (oxycodone), oxymorphone, plants and parts of plants belonging to the species *Papaver somniferum* (including the subspecies *setigerum*), papaveretum, 2-imino-5-phenyl-4-oxazolidinone (pernoline), 1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol (pentazocine), 5-ethyl-5-(1-methylbutyl)-barbituric acid (pentobarbital), ethyl-(1-methyl-4-phenyl-4-piperidine carboxylate) (pethidine), phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, pholcodine, 3-methyl-2-phenylmorpholine (phenmetrazine), 5-ethyl-5-phenylbarbituric acid (phenobarbital), α,α-dimethylphenethylamine (phentermine), 7-chloro-5-phenyl-1-(2-propynyl)-1H-1,4-benzodiazepine-2(3H)-one (pinazepam), α-(2-piperidyl)benzhydryl alcohol (pipradrol), 1'-(3-cyano-3,3-diphenylpropyl)[1,4'-bipiperidine]-4'-carboxamide (piritramide), 7-chloro-1-(cyclopropylmethyl)-5-phenyl-1H-1,4-benzodiazepine-2(3H)-one (prazepam), profadol, proheptazine, promedol, properidine, propoxyphene, N-(1-methyl-2-piperidinoethyl)-N-(2-pyridyl)propionamide, methyl {3-[4-methoxycarbonyl-4-(N-phenylpropanamido)piperidino]propanoate} (remifentanil), 5-sec-butyl-5-ethylbarbituric acid (secbutabarbital), 5-allyl-5-(1-methylbutyl)-barbituric acid (secobarbital), N-{4-methoxymethyl-1-[2-(2-thienyl)ethyl]-4-piperidyl}-propionanilide (sufentanil), 7-chloro-2-hydroxy-methyl-5-phenyl-1H-1,4-benzodiazepin-2(3H)-one (temazepam), 7-chloro-5-(1-cyclohexenyl)-1-methyl-1H-1,4-benzodiazepine-2(3H)-one (tetrazepam), ethyl(2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate) (tilidine (cis and trans)), tramadol, 8-chloro-6-(2-chlorophenyl)-1-methyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine (triazolam), 5-(1-methylbutyl)-5-vinylbarbituric acid (vinylbital), (1R*,2R*)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol, (1R,2R,4S)-2-(dimethylamino)methyl-4-(p-fluoro-benzyloxy)-1-(m-methoxyphenyl)cyclohexanol, (1R,2R)-3-(2-

dimethylaminomethyl-cyclohexyl)phenol, (1S,2S)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol, (2R,3R)-1-dimethylamino-3(3-methoxyphenyl)-2-methyl-pentan-3-ol, (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxyphenyl)-cyclohexane-1,3-diol, 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)phenyl 2-(4-isobutoxy-phenyl)-propionate, 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl) phenyl 2-(6-methoxy-naphthalen-2-yl)-propionate, 3-(2-dimethylamino-methyl-cyclohex-1-enyl)-phenyl 2-(4-isobutyl-phenyl)-propionate, 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(6-methoxy-naphthalen-2-yl)-propionate, (RR—SS)-2-acetoxy-4-trifluoromethyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR—SS)-2-hydroxy-4-trifluoromethyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR—SS)-4-chloro-2-hydroxy-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR—SS)-2-hydroxy-4-methyl-benzoic acid 3-(2-dimethylamino-methyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR—SS)-2-hydroxy-4-methoxy-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR—SS)-2-hydroxy-5-nitro-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR—SS)-2',4'-difluoro-3-hydroxy-biphenyl-4-carboxylic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester and for corresponding stereoisomeric compounds, the corresponding derivatives thereof in each case, in particular esters or ethers, and the physiologically acceptable compounds thereof in each case, in particular the salts and solvates thereof.

The compounds (1R*,2R*)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol, (1R,2R,4S)-2-(dimethylamino) methyl-4-(p-fluorobenzyloxy)-1-(m-methoxyphenyl)cyclohexanol or the stereoisomeric compounds thereof or the physiologically acceptable compounds thereof, in particular the hydrochlorides thereof, the derivatives thereof, such as esters or ethers, and processes for the production thereof are known, for example, from EP-A-693475 or EP-A-780369. The corresponding descriptions are hereby introduced as a reference and are deemed to be part of the disclosure.

In order to achieve the necessary breaking strength of the dosage form according to the invention, at least one synthetic or natural polymer (C) is used which has a breaking strength, measured using the method disclosed in the present application, of at least 500 N. At least one polymer selected from the group consisting of polymethylene oxide, polyethylene oxide, polypropylene oxide, polyethylene, polypropylene, polyvinyl chloride, polycarbonate, polystyrene, polyacrylate, copolymers thereof, and mixtures of at least two of the stated polymers is preferably used for this purpose. The polymers are distinguished by a molecular weight of at least 0.5 million, determined by rheological measurements. In one embodiment, the molecular weight ranges from 1-15 million. Thermoplastic polyalkylene oxides, such as polyethylene oxides, with a molecular weight of at least 0.5 million, preferably of up to 15 million, determined by rheological measurements, are very particularly preferred. These polymers have a viscosity at 25° C. of 4500 to 17600 cP, measured on a 5 wt. % aqueous solution using a model RVF Brookfield viscosimeter (spindle no. 2/rotational speed 2 rpm), of 400 to 4000 cP, measured on a 2 wt. % aqueous solution using the stated viscosimeter (spindle no. 1 or 3/rotational speed 10 rpm) or of 1650 to 10000 cP, measured on a 1 wt. % aqueous solution using the stated viscosimeter (spindle no. 2/rotational speed 2 rpm).

The polymers are used in powder form.

In order to achieve the necessary breaking strength of the dosage form according to the invention, it is furthermore possible additionally to use at least one natural or synthetic wax (D) with a breaking strength, measured using the method disclosed in the present application, of at least 500 N. Waxes with a softening point of at least 60° C. are preferred. Carnauba wax and beeswax are particularly preferred. Carnauba wax is very particularly preferred. Carnauba wax is a natural wax which is obtained from the leaves of the carnauba palm and has a softening point of ≧80° C. When the wax component is additionally used, it is used together with at least one polymer (C) in quantities such that the dosage form has a breaking strength of at least 500 N.

The dosage forms according to the invention are distinguished in that, due their hardness, they cannot be pulverised, for example by grinding in a mortar. This virtually rules out oral or parenteral, in particular intravenous or nasal abuse. However, in order to prevent any possible abuse in the event of comminution and/or pulverisation of the dosage form according to the invention which has nevertheless been achieved by application of extreme force, the dosage forms according to the invention may, in a preferred embodiment, contain further agents which complicate or prevent abuse as auxiliary substances (B).

The abuse-proofed dosage form according to the invention, which comprises, apart from one or more active ingredients with abuse potential, at least one hardening polymer (C) and optionally at least one wax (D), may accordingly also comprise at least one of the following components (a)-(f) as auxiliary substances (B):

(a) at least one substance which irritates the nasal passages and/or pharynx,
(b) at least one viscosity-increasing agent, which, with the assistance of a necessary minimum quantity of an aqueous liquid, forms a gel with the extract obtained from the dosage form, which gel preferably remains visually distinguishable when introduced into a further quantity of an aqueous liquid,
(c) at least one antagonist for each of the active ingredients with abuse potential,
(d) at least one emetic,
(e) at least one dye as an aversive agent,
(f) at least one bitter substance.

Components (a) to (f) are additionally each individually suitable for abuse-proofing the dosage form according to the invention. Accordingly, component (a) is preferably suitable for proofing the dosage form against nasal, oral and/or parenteral, preferably intravenous, abuse, component (b) is preferably suitable for proofing against parenteral, particularly preferably intravenous and/or nasal abuse, component (c) is preferably suitable for proofing against nasal and/or parenteral, particularly preferably intravenous, abuse, component (d) is preferably suitable for proofing against parenteral, particularly preferably intravenous, and/or oral and/or nasal abuse, component (e) is suitable as a visual deterrent against oral or parenteral abuse and component (f) is suitable for proofing against oral or nasal abuse. Combined use according to the invention of at least one of the above-stated components makes it possible still more effectively to prevent abuse of dosage forms according to the invention.

In one embodiment, the dosage form according to the invention may also comprise two or more of components (a)-(f) in a combination, preferably (a), (b) and optionally (c) and/or (f) and/or (e) or (a), (b) and optionally (d) and/or (f) and/or (e).

In another embodiment, the dosage form according to the invention may comprise all of components (a)-(f).

If the dosage form according to the invention comprises component (a) to counter abuse, substances which irritate the nasal passages and/or pharynx which may be considered according to the invention are any substances which, when administered via the nasal passages and/or pharynx, bring about a physical reaction which is either so unpleasant for the abuser that he/she does not wish to or cannot continue administration, for example burning, or physiologically counteracts taking of the corresponding active ingredient, for example due to increased nasal secretion or sneezing. These substances which conventionally irritate the nasal passages and/or pharynx may also bring about a very unpleasant sensation or even unbearable pain when administered parenterally, in particular intravenously, such that the abuser does not wish to or cannot continue taking the substance.

Particularly suitable substances which irritate the nasal passages and/or pharynx are those which cause burning, itching, an urge to sneeze, increased formation of secretions or a combination of at least two of these stimuli. Appropriate substances and the quantities thereof which are conventionally to be used are known per se to the skilled person or may be identified by simple preliminary testing.

The substance which irritates the nasal passages and/or pharynx of component (a) is preferably based on one or more constituents or one or more plant parts of at least one hot substance drug.

Corresponding hot substance drugs are known per se to the person skilled in the art and are described, for example, in "Pharmazeutische Biologie—Drogen und ihre Inhaltsstoffe" by Prof. Dr. Hildebert Wagner, 2nd., revised edition, Gustav Fischer Verlag, Stuttgart-New York, 1982, pages 82 et seq. The corresponding description is hereby introduced as a reference and is deemed to be part of the disclosure.

The dosage form according to the invention may preferably contain the plant parts of the corresponding hot substance drugs in a quantity of 0.01 to 30 wt. %, particularly preferably of 0.1 to 0.5 wt. %, in each case relative to the total weight dosage unit.

If one or more constituents of corresponding hot substance drugs are used, the quantity thereof in a dosage unit according to the invention preferably amounts to 0.001 to 0.005 wt. %, relative to the total weight of the dosage unit.

A dosage unit is taken to mean a separate or separable administration unit, such as for example a tablet or a capsule.

One or more constituents of at least one hot substance drug selected from the group consisting of Allii sativi bulbus (garlic), Asari rhizoma cum herba (*Asarum* root and leaves), Calami rhizoma (*calamus* root), Capsici fructus (*capsicum*), Capsici fructus acer (cayenne pepper), Curcumae longae rhizoma (turmeric root), Curcumae xanthorrhizae rhizoma (Javanese turmeric root), Galangae rhizoma (galangal root), Myristicae semen (nutmeg), *Piperis* nigri fructus (pepper), *Sinapis albae* semen (white mustard seed), *Sinapis* nigri semen (black mustard seed), Zedoariae rhizoma (zedoary root) and Zingiberis rhizoma (ginger root), particularly preferably from the group consisting of Capsici fructus (*capsicum*), Capsici fructus acer (cayenne pepper) and *Piperis* nigri fructus (pepper) may preferably be added as component (a) to the dosage form according to the invention.

The constituents of the hot substance drugs preferably comprise o-methoxy(methyl)phenol compounds, acid amide compounds, mustard oils or sulfide compounds or compounds derived therefrom.

Particularly preferably, at least one constituent of the hot substance drugs is selected from the group consisting of myristicin, elemicin, isoeugenol, β-asarone, safrole, gingerols, xanthorrhizol, capsaicinoids, preferably capsaicin, capsaicin derivatives, such as N-vanillyl-9E-octadecenamide, dihydrocapsaicin, nordihydrocapsaicin, homocapsaicin, norcapsaicin and nomorcapsaicin, piperine, preferably trans-piperine, glucosinolates, preferably based on non-volatile mustard oils, particularly preferably based on p-hydroxybenzyl mustard oil, methylmercapto mustard oil or methylsulfonyl mustard oil, and compounds derived from these constituents.

Another option for preventing abuse of the dosage form according to the invention consists in adding at least one viscosity-increasing agent as a further abuse-preventing component (b) to the dosage form, which, with the assistance of a necessary minimum quantity of an aqueous liquid, forms a gel with the extract obtained from the dosage form, which gel is virtually impossible to administer safely and preferably remains visually distinguishable when introduced into a further quantity of an aqueous liquid.

For the purposes of the present invention visually distinguishable means that the active ingredient-containing gel formed with the assistance of a necessary minimum quantity of aqueous liquid, when introduced, preferably with the assistance of a hypodermic needle, into a further quantity of aqueous liquid at 37° C., remains substantially insoluble and cohesive and cannot straightforwardly be dispersed in such a manner that it can safely be administered parenterally, in particular intravenously. The material preferably remains visually distinguishable for at least one minute, preferably for at least 10 minutes.

The increased viscosity of the extract makes it more difficult or even impossible for it to be passed through a needle or injected. If the gel remains visually distinguishable, this means that the gel obtained on introduction into a further quantity of aqueous liquid, for example by injection into blood, initially remains in the form of a largely cohesive thread, which, while it may indeed be broken up into smaller fragments, cannot be dispersed or even dissolved in such a manner that it can safely be administered parenterally, in particular intravenously. In combination with at least one optionally present component (a) to (e), this additionally leads to unpleasant burning, vomiting, bad flavour and/or visual deterrence.

Intravenous administration of such a gel would most probably result in obstruction of blood vessels, associated with serious embolism or even death of the abuser.

In order to verify whether a viscosity-increasing agent is suitable as component (b) for use in the dosage form according to the invention, the active ingredient is mixed with the viscosity-increasing agent and suspended in 10 ml of water at a temperature of 25° C. If this results in the formation of a gel which fulfils the above-stated conditions, the corresponding viscosity-increasing agent is suitable for preventing or averting abuse of the dosage forms according to the invention.

If component (b) is added to the dosage form according to the invention, one or more viscosity-increasing agents are used which are selected from the group consisting of microcrystalline cellulose with 11 wt. % carboxymethylcellulose sodium (Avicel® RC 591), carboxymethylcellulose sodium (Blanose®, CMC-Na C300P®, Frimulsion BLC-5®, Tylose C300 P®), polyacrylic acid (Carbopol® 980 NF, Carbopol® 981), locust bean flour (Cesagum® LA-200, Cesagum® LID/150, Cesagum® LN-1), pectins such as citrus pectin (Cesapectin® HM Medium Rapid Set), apple pectin, pectin from lemon peel, waxy maize starch (C*Gel 04201®), sodium alginate (Frimulsion ALG (E401)®), guar flour (Frimulsion BM®, Polygum 26/1-75®), iota carrageen (Frimulsion D021®), karaya gum, gellan gum (Kelcogel F®, Kelcogel LT100®), galactomannan (Meyprogat 150®), tara bean flour

(Polygum 43/1), propylene glycol alginate (Protanal-Ester SD-LB®), sodium hyaluronate, tragacanth, tara gum (Vidogum SP 200®), fermented polysaccharide welan gum (K1A96), xanthan gum (Xantural 180®). Xanthans are particularly preferred. The names stated in brackets are the trade names by which the materials are known commercially. In general, a quantity of 0.1 to 5 wt. % of the viscosity-increasing agent(s) is sufficient to fulfil the above-stated conditions.

The component (b) viscosity-increasing agents, where provided, are preferably present in the dosage form according to the invention in quantities of ≧5 mg per dosage unit, i.e. per administration unit.

In a particularly preferred embodiment of the present invention, the viscosity-increasing agents used as component (b) are those which, on extraction from the dosage form with the necessary minimum quantity of aqueous liquid, form a gel which encloses air bubbles. The resultant gels are distinguished by a turbid appearance, which provides the potential abuser with an additional optical warning and discourages him/her from administering the gel parenterally.

It is also possible to formulate the viscosity-increasing agent and the other constituents in the dosage form according to the invention in a mutually spatially separated arrangement.

In order to discourage and prevent abuse, the dosage form according to the invention may furthermore comprise component (c), namely one or more antagonists for the active ingredient or active ingredients with abuse potential, wherein the antagonists are preferably spatially separated from the remaining constituents of the invention dosage according to the form and, when correctly used, do not exert any effect.

Suitable antagonists for preventing abuse of the active ingredients are known per se to the person skilled in the art and may be present in the dosage form according to the invention as such or in the form of corresponding derivatives, in particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof.

If the active ingredient present in the dosage form is an opiate or an opioid, the antagonist used is preferably an antagonist selected from the group consisting of naloxone, naltrexone, nalmefene, nalid, nalmexone, nalorphine or naluphine, in each case optionally in the form of a corresponding physiologically acceptable compound, in particular in the form of a base, a salt or solvate. The corresponding antagonists, where component (c) is provided, are preferably used in a quantity of ≧10 mg, particularly preferably in a quantity of 10 to 100 mg, very particularly preferably in a quantity of 10 to 50 mg per dosage form, i.e. per administration unit.

If the dosage form according to the invention comprises a stimulant as active ingredient, the antagonist is preferably a neuroleptic, preferably at least one compound selected from the group consisting of haloperidol, promethazine, fluphenazine, perphenazine, levomepromazine, thioridazine, perazine, chlorpromazine, chlorprothixine, zuclopentixol, flupentixol, prothipendyl, zotepine, benperidol, pipamperone, melperone and bromperidol.

The dosage form according to the invention preferably comprises these antagonists in a conventional therapeutic dose known to the person skilled in the art, particularly preferably in a quantity of twice to four times the conventional dose per administration unit.

If the combination to discourage and prevent abuse of the dosage form according to the invention comprises component (d), it may comprise at least one emetic, which is preferably present in a spatially separated arrangement from the other components of the dosage form according to the invention and, when correctly used, is intended not to exert its effect in the body.

Suitable emetics for preventing abuse of an active ingredient are known per se to the person skilled in the art and may be present in the dosage form according to the invention as such or in the form of corresponding derivatives, in particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof.

An emetic based on one or more constituents of radix ipecacuanha (ipecac root), preferably based on the constituent emetine may preferably be considered in the dosage form according to the invention, as are, for example, described in "Pharmazeutische Biologie—Drogen und ihre Inhaltsstoffe" by Prof. Dr. Hildebert Wagner, 2nd, revised edition, Gustav Fischer Verlag, Stuttgart, New York, 1982. The corresponding literature description is hereby introduced as a reference and is deemed to be part of the disclosure.

The dosage form according to the invention may preferably comprise the emetic emetine as component (d), preferably in a quantity of ≧10 mg, particularly preferably of ≧20 mg and very particularly preferably in a quantity of ≧40 mg per dosage form, i.e. administration unit.

Apomorphine may likewise preferably be used as an emetic in the abuse-proofing according to the invention, preferably in a quantity of preferably ≧3 mg, particularly preferably of ≧5 mg and very particularly preferably of ≧7 mg per administration unit.

If the dosage form according to the invention contains component (e) as a further abuse-preventing auxiliary substance, the use of a such a dye brings about an intense coloration of a corresponding aqueous solution, in particular when the attempt is made to extract the active ingredient for parenteral, preferably intravenous administration, which coloration may act as a deterrent to the potential abuser. Oral abuse, which conventionally begins by means of aqueous extraction of the active ingredient, may also be prevented by this coloration. Suitable dyes and the quantities required for the necessary deterrence may be found in WO 03/015531, wherein the corresponding disclosure should be deemed to be part of the present disclosure and is hereby introduced as a reference.

If the dosage form according to the invention contains component (f) as a further abuse-preventing auxiliary substance, this addition of at least one bitter substance and the consequent impairment of the flavour of the dosage form additionally prevents oral and/or nasal abuse.

Suitable bitter substances and the quantities effective for use may be found in US-2003/0064099 A1, the corresponding disclosure of which should be deemed to be the disclosure of the present application and is hereby introduced as a reference. Suitable bitter substances are preferably aromatic oils, preferably peppermint oil, eucalyptus oil, bitter almond oil, menthol, fruit aroma substances, preferably aroma substances from lemons, oranges, limes, grapefruit or mixtures thereof, and/or denatonium benzoate.

The solid dosage form according to the invention is suitable to be taken orally or rectally, preferably orally. The orally administrable dosage form according to the invention may assume multiparticulate form, preferably in the form of microtablets, microcapsules, micropellets, granules, spheroids, beads or pellets, optionally packaged in capsules or pressed into tablets. The multiparticulate forms preferably have a size or size distribution in the range from 0.1 to 3 mm, particularly preferably in the range from 0.5 to 2 mm.

Depending on the desired dosage form, conventional auxiliary substances (B) are optionally also used for the formulation of the dosage form.

The solid, abuse-proofed dosage form according to the invention is preferably produced by mixing the components (A), (B), (C) and/optionally (D) and at least one of the optionally present further abuse-preventing components (a)-(f) and, optionally after granulation, press-forming the resultant mixture to yield the dosage form with preceding, simultaneous, or subsequent exposure to heat.

Mixing of components (A), (B), (C) and optionally (D) and of the optionally present further components (a)-(f) proceeds in a mixer known to the person skilled in the art. The mixer may, for example, be a roll mixer, shaking mixer, shear mixer or compulsory mixer.

The resultant mixture is preferably formed directly by application of pressure to yield the dosage form according to the invention with preceding, simultaneous or subsequent exposure to heat. The mixture may, for example, be formed into tablets by direct tabletting. In direct tabletting with simultaneous exposure to heat, the tabletting tool, i.e. bottom punch, top punch and die are briefly heated at least to the softening temperature of the polymer (C) and pressed together. In direct tabletting with subsequent exposure to heat, the formed tablets are briefly heated at least to the softening temperature (glass transition temperature, melting temperature; sintering temperature) of component (C) and cooled again. In direct tabletting with preceding exposure to heat, the material to be pressed is heated immediately prior to tabletting at least to the softening temperature of component (C) and then pressed.

The resultant mixture of components (A), (B), (C) and optionally (D) and the optionally present components (a) to (f) may also first be granulated and then be formed with preceding, simultaneous, or subsequent exposure to heat to yield the dosage form according to the invention.

In a further preferred embodiment, the dosage form according to the invention assumes the form of a tablet, a capsule or is in the form of an oral osmotic therapeutic system (OROS), preferably if at least one further abuse-preventing component (a)-(f) is also present.

If components (c) and/or (d) and/or (f) are present in the dosage form according to the invention, care must be taken to ensure that they are formulated in such a manner or are present in such a low dose that, when correctly administered, the dosage form is able to bring about virtually no effect which impairs the patient or the efficacy of the active ingredient.

If the dosage form according to the invention contains component (d) and/or (f), the dosage must be selected such that, when correctly orally administered, no negative effect is caused. If, however, the intended dosage of the dosage form is exceeded inadvertently, in particular by children, or in the event of abuse, nausea or an inclination to vomit or a bad flavour are produced. The particular quantity of component (d) and/or (f) which can still be tolerated by the patient in the event of correct oral administration may be determined by the person skilled in the art by simple preliminary testing.

If, however, irrespective of the fact that the dosage form according to the invention is virtually impossible to pulverise, the dosage form containing the components (c) and/or (d) and/or (f) is provided with protection, these components should preferably be used at a dosage which is sufficiently high that, when abusively administered, they bring about an intense negative effect on the abuser. This is preferably achieved by spatial separation of at least the active ingredient or active ingredients from components (c) and/or (d) and/or (f), wherein the active ingredient or active ingredients is/are present in at least one subunit (X) and components (c) and/or (d) and/or (f) is/are present in at least one subunit (Y), and wherein, when the dosage form is correctly administered, components (c), (d) and (f) do not exert their effect on taking and/or in the body and the remaining components of the formulation, in particular component (C), are identical.

If the dosage form according to the invention comprises at least 2 of components (c) and (d) or (f), these may each be present in the same or different subunits (Y). Preferably, when present, all the components (c) and (d) and (f) are present in one and the same subunit (Y).

For the purposes of the present invention, subunits are solid formulations, which in each case, apart from conventional auxiliary substances known to the person skilled in the art, contain the active ingredient(s), at least one polymer (C) and optionally at least one of the optionally present components (a) and/or (b) and/or (e) or in each case at least one polymer (C) and the antagonist(s) and/or emetic(s) and/or component (e) and/or component (f) and optionally at least one of the optionally present components (a) and/or (b). Care must here be taken to ensure that each of the subunits is formulated in accordance with the above-stated process.

One substantial advantage of the separated formulation of active ingredients from components (c) or (d) or (f) in subunits (X) and (Y) of the dosage form according to the invention is that, when correctly administered, components (c) and/or (d) and/or (f) are hardly released on taking and/or in the body or are released in such small quantities that they exert no effect which impairs the patient or therapeutic success or, on passing through the patient's body, they are only liberated in locations where they cannot be sufficiently absorbed to be effective. When the dosage form is correctly administered, hardly any of components (c) and/or (d) and/or (f) is released into the patient's body or they go unnoticed by the patient.

The person skilled in the art will understand that the above-stated conditions may vary as a function of the particular components (c), (d) and/or (f) used and of the formulation of the subunits or the dosage form. The optimum formulation for the particular dosage form may be determined by simple preliminary testing. What is vital is that each subunit contains the polymer (C) and has been formulated in the stated manner.

Should, contrary to expectations, the abuser succeed in comminuting such a dosage form according to the invention, which comprises components (c) and/or (e) and/or (d) and/or (f) in subunits (Y), for the purpose of abusing the active ingredient and obtain a powder which is extracted with a suitable extracting agent, not only the active ingredient but also the particular component (c) and/or (e) and/or (f) and/or (d) will be obtained in a form in which it cannot readily be separated from the active ingredient, such that when the dosage form which has been tampered with is administered, in particular by oral and/or parenteral administration, it will exert its effect on taking and/or in the body combined with an additional negative effect on the abuser corresponding to component (c) and/or (d) and/or (f) or, when the attempt is made to extract the active ingredient, the coloration will act as a deterrent and so prevent abuse of the dosage form.

A dosage form according to the invention, in which the active ingredient or active ingredients is/are spatially separated from components (c), (d) and/or (e), preferably by formulation in different subunits, may be formulated in many different ways, wherein the corresponding subunits may each be present in the dosage form according to the invention in any desired spatial arrangement relative to one another, pro-

vided that the above-stated conditions for the release of components (c) and/or (d) are fulfilled.

The person skilled in the art will understand that component(s) (a) and/or (b) which are optionally also present may preferably be formulated in the dosage form according to the invention both in the particular subunits (X) and (Y) and in the form of independent subunits corresponding to subunits (X) and (Y), provided that neither the abuse-proofing nor the active ingredient release in the event of correct administration is impaired by the nature of the formulation and the polymer (C) is included in the formulation and formulation is carried out in accordance with the above-stated process.

In a preferred embodiment of the dosage form according to the invention, subunits (X) and (Y) are present in multiparticulate form, wherein microtablets, microcapsules, micropellets, granules, spheroids, beads or pellets are preferred and the same form, i.e. shape, is selected for both subunit (X) and subunit (Y), such that it is not possible to separate subunits (X) from (Y) by mechanical selection. The multiparticulate forms are preferably of a size in the range from 0.1 to 3 mm, preferably of 0.5 to 2 mm.

The subunits (X) and (Y) in multiparticulate form may also preferably be packaged in a capsule or be pressed into a tablet, wherein the final formulation in each case proceeds in such a manner that the subunits (X) and (Y) are also retained in the resultant dosage form.

The multiparticulate subunits (X) and (Y) of identical shape should also not be visually distinguishable from one another so that the abuser cannot separate them from one another by simple sorting. This may, for example, be achieved by the application of identical coatings which, apart from this disguising function, may also incorporate further functions, such as, for example, controlled release of one or more active ingredients or provision of a finish resistant to gastric juices on the particular subunits.

In a further preferred embodiment of the present invention, subunits (X) and (Y) are in each case arranged in layers relative to one another.

The layered subunits (X) and (Y) are preferably arranged for this purpose vertically or horizontally relative to one another in the dosage form according to the invention, wherein in each case one or more layered subunits (X) and one or more layered subunits (Y) may be present in the dosage form, such that, apart from the preferred layer sequences (X)-(Y) or (X)-(Y)-(X), any desired other layer sequences may be considered, optionally in combination with layers containing components (a) and/or (b).

Another preferred dosage form according to the invention is one in which subunit (Y) forms a core which is completely enclosed by subunit (X), wherein a separation layer (Z) may be present between said layers. Such a structure is preferably also suitable for the above-stated multiparticulate forms, wherein both subunits (X) and (Y) and an optionally present separation layer (Z), which must satisfy the hardness requirement according to the invention, are formulated in one and the same multiparticulate form. In a further preferred embodiment of the dosage form according to the invention, the subunit (X) forms a core, which is enclosed by subunit (Y), wherein the latter comprises at least one channel which leads from the core to the surface of the dosage form.

The dosage form according to the invention may comprise, between one layer of the subunit (X) and one layer of the subunit (Y), in each case one or more, preferably one, optionally swellable separation layer (Z) which serves to separate subunit (X) spatially from (Y).

If the dosage form according to the invention comprises the layered subunits (X) and (Y) and an optionally present separation layer (Z) in an at least partially vertical or horizontal arrangement, the dosage form preferably takes the form of a tablet, a coextrudate or a laminate.

In one particularly preferred embodiment, the entirety of the free surface of subunit (Y) and optionally at least part of the free surface of subunit(s) (X) and optionally at least part of the free surface of the optionally present separation layer(s) (Z) may be coated with at least one barrier layer (Z') which prevents release of component (c) and/or (e) and/or (d) and/or (f). The barrier layer (Z') must also fulfil the hardness conditions according to the invention.

Another particularly preferred embodiment of the dosage form according to the invention comprises a vertical or horizontal arrangement of the layers of subunits (X) and (Y) and at least one push layer (p) arranged therebetween, and optionally a separation layer (Z), in which dosage form the entirety of the free surface of layer structure consisting of subunits (X) and (Y), the push layer and the optionally present separation layer (Z) is provided with a semipermeable coating (E), which is permeable to a release medium, i.e. conventionally a physiological liquid, but substantially impermeable to the active ingredient and to component (c) and/or (d) and/or (f), and wherein this coating (E) comprises at least one opening for release of the active ingredient in the area of subunit (X).

A corresponding dosage form is known to the person skilled in the art, for example under the name oral osmotic therapeutic system (OROS), as are suitable materials and methods for the production thereof, inter alia from U.S. Pat. No. 4,612,008, U.S. Pat. No. 4,765,989 and U.S. Pat. No. 4,783,337. The corresponding descriptions are hereby introduced as a reference and are deemed to be part of the disclosure.

In a further preferred embodiment, the subunit (X) of the dosage form according to the invention is in the form of a tablet, the edge face of which and optionally one of the two main faces is covered with a barrier layer (Z') containing component (c) and/or (d) and/or (f).

The person skilled in the art will understand that the auxiliary substances of the subunit(s) (X) or (Y) and of the optionally present separation layer(s) (Z) and/or of the barrier layer(s) (Z') used in formulating the dosage form according to the invention will vary as a function of the arrangement thereof in the dosage form according to the invention, the mode of administration and as a function of the particular active ingredient of the optionally present components (a) and/or (b) and/or (e) and of component (c) and/or (d) and/or (f). The materials which have the requisite properties are in each case known per se to the person skilled in the art.

If release of component (c) and/or (d) and/or (f) from subunit (Y) of the dosage form according to the invention is prevented with the assistance of a cover, preferably a barrier layer, the subunit may consist of conventional materials known to the person skilled in the art, providing that it contains at least one polymer (C) to fulfil the hardness condition of the dosage form according to the invention.

If a corresponding barrier layer (Z') is not provided to prevent release of component (c) and/or (d) and/or (f), the materials of the subunits should be selected such that release of the particular component (c) and/or (d) from subunit (Y) is virtually ruled out. The materials which are stated below to be suitable for production of the barrier layer may preferably be used for this purpose. The materials for the separation layer and/or barrier layer must contain at least one polymer (C) in order to fulfil the hardness conditions.

Preferred materials are those which are selected from the group consisting of alkylcelluloses, hydroxyalkylcelluloses, glucans, scleroglucans, mannans, xanthans, copolymers of

poly[bis(p-carboxyphenoxy)propane and sebacic acid, preferably in a molar ratio of 20:80 (commercially available under the name Polifeprosan 20®), carboxymethylcelluloses, cellulose ethers, cellulose esters, nitrocelluloses, polymers based on (meth)acrylic acid and the esters thereof, polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, halogenated polyvinyls, polyglycolides, polysiloxanes and polyurethanes and the copolymers thereof.

Particularly suitable materials may be selected from the group consisting of methylcellulose, ethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxybutylmethylcellulose, cellulose acetate, cellulose propionate (of low, medium or high molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxymethylcellulose, cellulose triacetate, sodium cellulose sulfate, polymethyl methacrylate, polyethyl methacrylate, polybutyl methacrylate, polyisobutyl methacrylate, polyhexyl methacrylate, polyisodecyl methacrylate, polylauryl methacrylate, polyphenyl methacrylate, polymethyl acrylate, polyisopropyl acrylate, polyisobutyl acrylate, polyoctadecyl acrylate, polyethylene, low density polyethylene, high density polyethylene, polypropylene, polyethylene glycol, polyethylene oxide, polyethylene terephthalate, polyvinyl alcohol, polyvinyl isobutyl ether, polyvinyl acetate and polyvinyl chloride.

Particularly suitable copolymers may be selected from the group consisting of copolymers of butyl methacrylate and isobutyl methacrylate, copolymers of methyl vinyl ether and maleic acid with high molecular weight, copolymers of methyl vinyl ether and maleic acid monoethyl ester, copolymers of methyl vinyl ether and maleic anhydride and copolymers of vinyl alcohol and vinyl acetate.

Further materials which are particularly suitable for formulating the barrier layer are starch-filled polycaprolactone (WO98/20073), aliphatic polyesteramides (DE 19 753 534 A1, DE 19 800 698 A1, EP 0 820 698 A1), aliphatic and aromatic polyester urethanes (DE 19822979), polyhydroxyalkanoates, in particular polyhydroxybutyrates, polyhydroxyvalerates, casein (DE 4 309 528), polylactides and copolylactides (EP 0 980 894 A1). The corresponding descriptions are hereby introduced as a reference and are deemed to be part of the disclosure.

The above-stated materials may optionally be blended with further conventional auxiliary substances known to the person skilled in the art, preferably selected from the group consisting of glyceryl monostearate, semi-synthetic triglyceride derivatives, semi-synthetic glycerides, hydrogenated castor oil, glyceryl palmitostearate, glyceryl behenate, polyvinylpyrrolidone, gelatine, magnesium stearate, stearic acid, sodium stearate, talcum, sodium benzoate, boric acid and colloidal silica, fatty acids, substituted triglycerides, glycerides, polyoxyalkylene glycols and the derivatives thereof.

If the dosage form according to the invention comprises a separation layer (Z'), said layer, like the uncovered subunit (Y), may preferably consist of the above-stated materials described for the barrier layer. The person skilled in the art will understand that release of the active ingredient or of component (c) and/or (d) from the particular subunit may be controlled by the thickness of the separation layer.

The dosage form according to the invention may comprise one or more active ingredients at least partially in controlled release form, wherein controlled release may be achieved with the assistance of conventional materials and methods known to the person skilled in the art, for example by embedding the active ingredient in a controlled release matrix or by the application of one or more controlled release coatings. Active ingredient release must, however, be controlled such that the above-stated conditions are fulfilled in each case, for example that, in the event of correct administration of the dosage form, the active ingredient or active ingredients are virtually completely released before the optionally present component (c) and/or (d) can exert an impairing effect.

Controlled release from the dosage form according to the invention is preferably achieved by embedding the active ingredient in a matrix. The auxiliary substances acting as matrix materials control active ingredient release. Matrix materials may, for example, be hydrophilic, gel-forming materials, from which active ingredient release proceeds mainly by diffusion, or hydrophobic materials, from which active ingredient release proceeds mainly by diffusion from the pores in the matrix.

Physiologically acceptable, hydrophobic materials which are known to the person skilled in the art may be used as matrix materials. Polymers, particularly preferably cellulose ethers, cellulose esters and/or acrylic resins are preferably used as hydrophilic matrix materials. Ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxymethylcellulose, poly(meth)acrylic acid and/or the derivatives thereof, such as the salts, amides or esters thereof are very particularly preferably used as matrix materials.

Matrix materials prepared from hydrophobic materials, such as hydrophobic polymers, waxes, fats, long-chain fatty acids, fatty alcohols or corresponding esters or ethers or mixtures thereof are also preferred. Mono- or diglycerides of C12-C30 fatty acids and/or C12-C30 fatty alcohols and/or waxes or mixtures thereof are particularly preferably used as hydrophobic materials.

It is also possible to use mixtures of the above-stated hydrophilic and hydrophobic materials as matrix materials.

Component (C) and the optionally present component (D), which serve to achieve the breaking strength of at least 500 N which is necessary according to the invention may furthermore also optionally serve as additional matrix materials.

If the dosage form according to the invention is intended for oral administration, it may also preferably comprise a coating which is resistant to gastric juices and dissolves as a function of the pH value of the release environment. By means of this coating, it is possible to ensure that the dosage form according to the invention passes through the stomach undissolved and the active ingredient is only released in the intestines. The coating which is resistant to gastric juices preferably dissolves at a pH value of between 5 and 7.5.

Corresponding materials and methods for the controlled release of active ingredients and for the application of coatings which are resistant to gastric juices are known to the person skilled in the art, for example from "Coated Pharmaceutical Dosage Forms—Fundamentals, Manufacturing Techniques, Biopharmaceutical Aspects, Test Methods and Raw Materials" by Kurt H. Bauer, K. Lehmann, Hermann P. Osterwald, Rothgang, Gerhart, 1st edition, 1998, Medpharm Scientific Publishers. The corresponding literature description is hereby introduced as a reference and is deemed to be part of the disclosure.

Method for Determining Breaking Strength

A) In order to verify whether a polymer may be used as component (C), the polymer is pressed to form a tablet with a diameter of 10 mm and a height of 5 mm using a force of 150 N at a temperature which at least corresponds to the softening point of the polymer and is determined with the assistance of a DSC diagram of the polymer. Using tablets produced in this manner, breaking strength is determined with the apparatus described below in accordance with the method for determin-

ing the breaking strength of tablets published in the European Pharmacopoeia 1997, page 143-144, method no. 2.9.8. The apparatus used for the measurement is a series 3300 universal tester, single column benchtop model no. 3345 from Instron®, Canton, Mass., USA. The clamping tool used is a pressure piston with a diameter of 25 mm, which can be subjected to a load of up to 1 kN (item no. 2501-3 from Instron®).

An Instron® universal tester, single column benchtop model no. 5543, with the above-stated clamping tool may also be used to carry out the measurement.

The tablets deemed to be resistant to breaking under a specific load include not only those which have not broken but also those which may have suffered plastic deformation under the action of the force.

Providing that the dosage form is in tablet form, breaking strength may be determined using the same measurement method.

The following Examples illustrate the invention purely by way of example and without restricting the general concept of the invention.

EXAMPLES

Tramadol hydrochloride was used as the active ingredient in a series of Examples. Tramadol hydrochloride was used, despite tramadol not being an active ingredient which conventionally has abuse potential, because it is not governed by German narcotics legislation, so simplifying the experimental work. Tramadol is moreover a member of the opioid class with excellent water solubility.

Example 1

Components	Per tablet	Complete batch
Tramadol hydrochloride	100 mg	100 g
Polyethylene oxide, NF, MFI (190° C. at 21.6 kg/10 min) <0.5 g MW 7 000 000 (Polyox WSR 303, Dow Chemicals)	200 mg	200 g
Total weight	300 mg	300 g

Tramadol hydrochloride and polyethylene oxide powder were mixed in a free-fall mixer. A tabletting tool with top punch, bottom punch and die for tablets with a diameter of 10 mm and a radius of curvature of 8 mm was heated to 80° C. in a heating cabinet. 300 mg portions of the powder mixture were pressed with the heated tool, wherein pressure was maintained for at least 15 seconds by clamping the tabletting tool in a vice.

The breaking strength of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not break when exposed to a force of 500 N. The tablet could not be comminuted using a hammer, nor with the assistance of a mortar and pestle.

In vitro release of the active ingredient from the preparation was determined in a paddle stirrer apparatus in accordance with Pharm. Eur. The temperature of the release medium was 37° C. and the rotational speed of the stirrer 75 min^{-1}. At the beginning of the investigation, each tablet was placed in a 600 ml portion of artificial gastric juice, pH 1.2. After 30 minutes, the pH value was increased to 2.3 by addition of alkali solution, after a further 90 minutes to pH 6.5 and after a further 60 minutes to pH 7.2. The released quantity of active ingredient present in the dissolution medium at each point in time was determined by spectrophotometry.

Time	Released quantity
30 min	15%
240 min	52%
480 min	80%
720 min	99%

Example 2

300 mg portions of the powder mixture from Example 1 were heated to 80° C. and in placed in the die of the tabletting tool. Pressing was then performed. The tablet exhibits the same properties such as the tablet in Example 1.

Example 3

Raw material	Per tablet	Complete batch
Tramadol hydrochloride	50 mg	100 g
Polyethylene oxide, NF, MW 7 000 000 (Polyox WSR 303, Dow Chemicals)	100 mg	200 g
Total weight	150 mg	300 g

Tramadol hydrochloride and the above-stated components were mixed in a free-fall mixer. A tabletting tool with top punch, bottom punch and die for tablets with a diameter of 7 mm was heated to 80° C. in a heating cabinet. 150 mg portions of the powder mixture were pressed with the heated tool, wherein pressure was maintained for at least 15 seconds by clamping the tabletting tool in a vice.

The breaking strength of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not break when exposed to a force of 500 N.

In vitro release of the active ingredient was determined as in Example 1 and was:

Time	Released quantity
30 min	15%
240 min	62%
480 min	88%
720 min	99%

Example 4

Raw material	Per tablet	Complete batch
Tramadol hydrochloride	100 mg	100 g
Polyethylene oxide, NF, MW 7 000 000 (Polyox WSR	180 mg	180 g

-continued

Raw material	Per tablet	Complete batch
303, Dow Chemicals)		
Xanthan, NF	20 mg	20 g
Total weight	300 mg	300 g

Tramadol hydrochloride, xanthan and polyethylene oxide were mixed in a free-fall mixer. A tabletting tool with top punch, bottom punch and die for tablets with a diameter of 10 mm and a radius of curvature of 8 mm was heated to 80° C. in a heating cabinet. 300 mg portions of the powder mixture were pressed with the heated tool, wherein pressure was maintained for at least 15 seconds by clamping the tabletting tool in a vice.

The breaking strength of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not break when exposed to a force of 500 N. The tablets did suffer a little plastic deformation.

In vitro release of the active ingredient was determined as in Example 1 and was:

Time	Released quantity
30 min	14%
240 min	54%
480 min	81%
720 min	99%

The tablets could be cut up with a knife into pieces of an edge length of as small as approx. 2 mm. No further comminution proceeding as far as pulverisation was possible. When the pieces are combined with water, a highly viscous gel is formed. Only with great difficulty could the gel be pressed through a 0.9 mm injection cannula. When the gel was injected into water, the gel did not spontaneously mix with water, but remained visually distinguishable.

Example 5

Raw material	Per tablet	Complete batch
Tramadol hydrochloride	50 mg	100 g
Polyethylene oxide, NF, MW 7 000 000 (Polyox WSR 303, Dow Chemicals)	90 mg	180 g
Xanthan, NF	10 mg	20 g
Total weight	300 mg	300 g

Tramadol hydrochloride, xanthan and polyethylene oxide were mixed in a free-fall mixer. A tabletting tool with a top punch, bottom punch and die for oblong tablets 10 mm in length and 5 mm in width was heated to 90° C. in a heating cabinet. 150 mg portions of the powder mixture were pressed with the heated tool, wherein pressure was maintained for at least 15 seconds by clamping the tabletting tool in a vice.

The breaking strength of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not break when exposed to a force of 500 N. The tablets did suffer a little plastic deformation.

In vitro release of the active ingredient was determined as in Example 1 and was:

Time	Released quantity
30 min	22%
120 min	50%
240 min	80%
360 min	90%
480 min	99%

The tablets could be cut up into pieces of an edge length of as small as approx. 2 mm, but could not be pulverised. When the pieces are combined with water, a highly viscous gel is formed. Only with great difficulty could the gel be pressed through a 0.9 mm injection cannula. When the gel was injected into water, the gel did not spontaneously mix with water, but remained visually distinguishable.

Example 6

A tablet with the following composition was produced as described in Example 1:

Components	Per tablet	Per batch
Oxycodone hydrochloride	20.0 mg	0.240 g
Xanthan, NF	20.0 mg	0.240 g
Polyethylene oxide, NF, MFI (190° C. at 21.6 kg/10 min) <0.5 g MW 7 000 000 (Polyox WSR 303, Dow Chemicals)	110.0 mg	1.320 g
Total weight	150.0 mg	1.800 g

Release of the active ingredient was determined as follows:

In vitro release of the active ingredient from the preparation was determined in a paddle stirrer apparatus in accordance with Pharm. Eur. The temperature of the release medium was 37° C. and the rotational speed 75 rpm. The phosphate buffer, pH 6.8, described in DSP served as the release medium. The quantity of active ingredient present in the solvent at the particular time of testing was determined by spectrophotometry.

Time	Mean
0 min	0%
30 min	17%
240 min	61%
480 min	90%
720 min	101.1%

The breaking strength of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not break when exposed to a force of 500 N.

The tablets could be cut up into pieces of an edge length of as small as approx. 2 mm, but could not be pulverised. When the pieces are combined with water, a highly viscous gel is formed. Only with great difficulty could the gel be pressed through a 0.9 mm injection cannula. When the gel was injected into water, the gel did not spontaneously mix with water, but remained visually distinguishable.

What is claimed is:

1. A thermoformed dosage form comprising:

i) one or more active ingredients with abuse potential (A) selected from the group consisting of opiates and opioids,

ii) optionally physiologically acceptable auxiliary substances (B),

iii) at least 30% by weight of polyalkylene oxide (C) having a molecular weight of 1-15 million according to rheological measurements, and

iv) optionally at least one wax (D),

wherein said dosage form has a breaking strength of at least 500 N and wherein the active ingredient with abuse potential (A) is present in a controlled release matrix of component (C).

2. The dosage form according to claim **1**, which is in the form of a tablet.

3. The dosage form according to claim **1**, wherein the wax (D) is at least one natural, semi-synthetic or synthetic wax with a softening point of at least 60° C.

4. The dosage form according to claim **3**, wherein the wax (D) is carnauba wax or beeswax.

5. A process for the production of a dosage form according to claim **1**, said process comprising mixing components (A), the optionally present component (B), component (C) and the optionally present component (D) to form a mixture and, optionally after granulation, press-forming the mixture with preceding, simultaneous, or subsequent exposure to heat.

6. A process according to claim **5**, wherein granulation is performed by means of a melt process.

7. A dosage form obtained by the process of claim **5**.

8. The dosage form according to claim **1**, wherein the active ingredient with abuse potential (A) is oxycodone or a physiologically acceptable salt thereof.

9. The dosage form according to claim **1**, wherein the active ingredient with abuse potential (A) is oxymorphone or a physiologically acceptable salt thereof.

* * * * *